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FeCl$_3$-Catalyzed 1,2-Addition Reactions of Aryl Aldehydes with Arylboronic Acids

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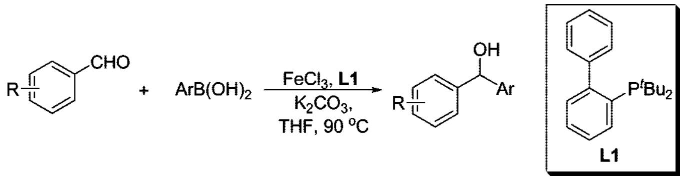
ABSTRACT



A novel protocol for the 1,2-addition reactions of electron-deficient aryl aldehydes with arylboronic acids using an inexpensive and environmentally benign iron catalyst is reported. In the presence of FeCl$_3$ and 2-(di-*tert*-butylphosphino)biphenyl, 1,2-addition reactions of various electron-deficient aryl aldehydes with arylboronic acids provided the corresponding biaryl methanols in moderate to excellent yields.

Rhodium-catalyzed 1,2-addition of aldehydes with organoboronic acids was first reported by Miyaura in 1998. Shortly after, other transition-metal-catalyzed versions of this transformation emerged, and the method quickly became a valuable tool for carbon−carbon bond formation.[1−6] However, these transformations are often used highly expensive transition metal catalysts, such as rhodium,[1,2] palladium,[3] platinum,[4] and nickel[5] complexes. Only one paper has reported on the use of inexpensive copper catalyst.[6] In view of both economy and environment, a great challenge still remains regarding the use of some inexpensive and environmentally benign catalysts for the 1,2-addition reaction. Recently, iron, an inexpensive and environmentally benign catalyst, has been proven to be efficient for the formation of carbon−carbon and carbon−heteroatom bonds.[7] A representative example is that iron displayed highly

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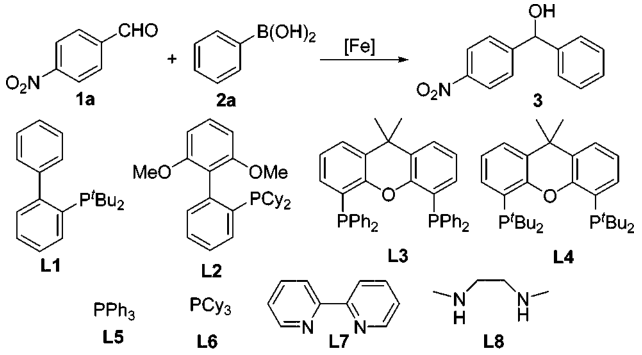
catalytic activation in the addition reactions of carbonyl compounds with normal O-, N-, S-, P-, or C-nucleophiles.[7,8] Prompted by these results, we decided to evaluate the feasibility of iron-catalyzed 1,2-addition reactions of aldehydes with nucleophilic organoboronic acids. To our delight, we found that $FeCl_3$ combined with 2-(di-*tert*-butylphosphino)biphenyl was an efficient catalytic system for the 1,2-addition reactions of electron-deficient aryl aldehydes with arylboronic acids. Here, we wish to report our preliminary results on the first example of iron-catalyzed 1,2-addition of aldehydes with organoboronic acids.

The effect of several ligands was initially tested in the 1,2-addition reaction of 4-nitrobenzaldehyde (**1a**) with phenylboronic acid (**2a**) using $FeCl_3$ as the catalyst (Table 1). Without ligands, treatment of substrate **1a** with boronic acid **2a**, $FeCl_3$, and K_2CO_3 afforded a trace amount of the target product **3** determined by GC−MS analysis (entry 1). The yield of **3** was enhanced sharply to 97% in the presence of 2-(di-*tert*-butylphosphino)biphenyl (**L1**) (entry 2). However, other ligands **L2**−**L8** were less active (entries 3−9). Subsequently, both bases and solvents were evaluated (entries 10−14). We found that another base, CsF, decreased the yield (entry 10), and other solvents, including dioxane, benzene, or MeCN, were unsuitable media for the reaction (entries 12−14). It is noted that no reaction takes place without either bases or iron catalysts (entries 11 and 15). The controlled experiments showed that other Fe catalysts, such as FeF_3, $Fe(SO_4)_3$, $Fe(NO_3)_3$, and $FeCl_2$, were less efficient than $FeCl_3$ (entries 16−19). Although the yield was reduced to some extent, both FeF_3 and $Fe(SO_4)_3$ are still highly active. However, $Fe(NO_3)_3$ and $FeCl_2$ have no effect on the reaction. Finally, amounts of $FeCl_3$, ligand, and phenylboronic acid were examined (entries 20−22). We were happy to find that a good yield of **3** was still achieved even at a loading of 5 mol % $FeCl_3$ (entry 20), and the increased loading of **L1** did not affect the yield (entry 21). However, the yield was reduced to 60% in the presence of 1.2 equiv of phenylboronic acid (**2a**) (entry 22). A good yield was still obtained using a $Rh(PPh_3)_3Cl$/**L1** catalytic system (entry 23).

Table 1. Iron-Catalyzed 1,2-Addition of 4-Nitrobenzaldehyde (**1a**) with Phenylboronic Acid (**2a**)[a]



entry	[Fe]	ligand	solvent	base	yield (%)[b]
1	$FeCl_3$		THF	K_2CO_3	trace
2	$FeCl_3$	**L1**	THF	K_2CO_3	97
3	$FeCl_3$	**L2**	THF	K_2CO_3	trace
4	$FeCl_3$	**L3**	THF	K_2CO_3	trace
5	$FeCl_3$	**L4**	THF	K_2CO_3	8
6	$FeCl_3$	**L5**	THF	K_2CO_3	trace
7	$FeCl_3$	**L6**	THF	K_2CO_3	trace
8	$FeCl_3$	**L7**	THF	K_2CO_3	trace
9	$FeCl_3$	**L8**	THF	K_2CO_3	trace
10	$FeCl_3$	**L1**	THF	CsF	85
11	$FeCl_3$	**L1**	THF		0
12	$FeCl_3$	**L1**	dioxane	K_2CO_3	trace
13	$FeCl_3$	**L1**	benzene	K_2CO_3	5
14	$FeCl_3$	**L1**	MeCN	K_2CO_3	trace
15		**L1**	THF	K_2CO_3	0
16	FeF_3	**L1**	THF	K_2CO_3	92
17	$Fe(SO_4)_3$	**L1**	THF	K_2CO_3	82
18	$Fe(NO_3)_3$	**L1**	THF	K_2CO_3	trace
19	$FeCl_2$	**L1**	THF	K_2CO_3	trace
20[c]	$FeCl_3$	**L1**	THF	K_2CO_3	91
21[d]	$FeCl_3$	**L1**	THF	K_2CO_3	98
22[e]	$FeCl_3$	**L1**	THF	K_2CO_3	60
23[f]	$Rh(PPh_3)_3Cl$	**L1**	THF	K_2CO_3	80

[a] Reaction conditions: **1** (0.25 mmol), **2a** (2 equiv), $FeCl_3$ (10 mol %), ligand (10 mol %), and base (2 equiv) in solvent (2 mL) at 90 °C for 22−24 h. [b] Isolated yield. [c] $FeCl_3$ (5 mol %). [d] **L1** (20 mol %) was added. [e] 1.2 equiv of $PhB(OH)_2$ **2a** was added. [f] $Rh(PPh_3)_3Cl$ (2 mol%) instead of $FeCl_3$.

As shown in Table 2, both aryl aldehydes and arylboronic acids were surveyed to investigate the scope of the reaction under the standard reaction conditions. The results showed that an electronic effect of the functional groups both in aryl aldehydes and arylboronic acids plays an important role in the reaction. We found that only electron-deficient aryl aldehydes could undergo the reaction with either electron-rich or electron-neutral arylboronic acids in moderate to excellent yields, but with electron-deficient arylboronic acids the reaction gave low yields. Initially, a variety of arylboronic acids were examined by reacting with 4-nitrobenzaldehyde (**1a**), $FeCl_3$, and **L1** (entries 1−7). To our delight, a number of functional groups, including methyl, methoxy, fluoro, chloro, and acetyl groups, were tolerated well. Boronic acids **2a** and **2c** bearing a *p*- or *o*-methyl group, for instance, were reacted with substrate **1a**, $FeCl_3$, and **L1** smoothly in excellent yields (entries 1 and 3), and boronic acids **2c** having a *m*-methyl group gave a moderate yield (entry 2). The reaction conditions are also compatible with ether, halide, and acetyl groups that could be readily substituted and decomposed under harsh conditions (entries 4−7). While boronic acid **2f** containing a *p*-fluoro group, for example, was treated with substrate **1a**, $FeCl_3$, and **L1** successfully in quantitative yield (entry 5), two other electro-deficient

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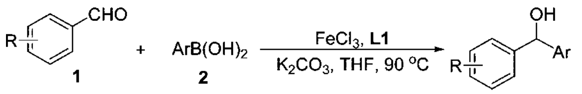
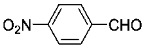
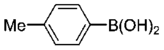
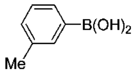
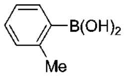
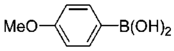
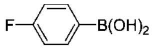
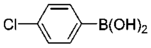
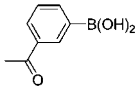
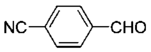
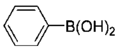
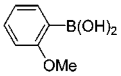
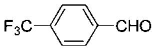
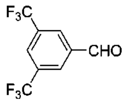
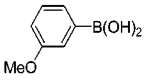
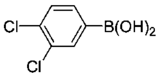
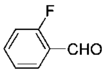
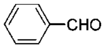
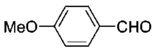
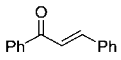
(8) For detailed iron-catalyzed carbonyl compounds with C-nucleophiles, see: Christoffers, J.; Frey, H.; Rosiak, A. In *Iron Catalysis in Organic Chemistry: Reactions and Applications*; Plietker, B. Ed.; Wiley-VCH: Weinheim, 2008; pp 217−243.

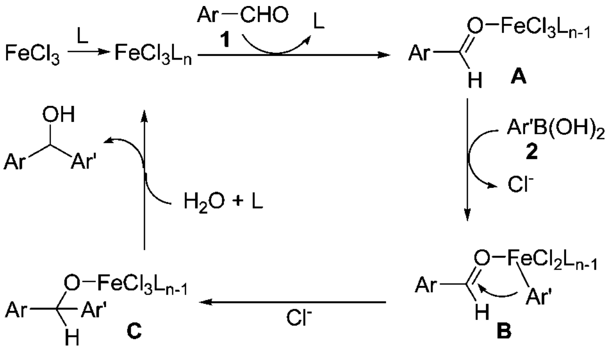
Table 2. $FeCl_3$-Catalyzed 1,2-Addition of Aryl Aldehyde (**1**) with Arylboronic Acid (**2**) in the Presence of 2-(Di-*tert*-butylphosphino)biphenyl (**L1**)[a]



Entry	Aldehyde	$ArB(OH)_2$	Yield (%)[b]
1	 (**1a**)	 (**2b**)	95 (**4**)
2	**1a**	 (**2c**)	71 (**5**)
3	**1a**	 (**2d**)	99 (**6**)
4[c]	**1a**	 (**2e**)	99 (**7**)
5	**1a**	 (**2f**)	99 (**8**)
6	**1a**	 (**2g**)	32 (**9**)
7	**1a**	 (**2h**)	34 (**10**)
8	 (**1b**)	 (**2a**)	97 (**11**)
9	**1b**	 (**2i**)	99 (**12**)
10	 (**1c**)	**2a**	99 (**13**)
11	**1c**	**2b**	98 (**14**)
12	**1c**	**2e**	99 (**15**)
13	**1c**	**2i**	99 (**16**)
14	 (**1d**)	**2a**	91 (**17**)
15	**1d**	**2b**	91 (**18**)
16	**1d**	**2e**	97 (**19**)
17	**1d**	**2i**	93 (**20**)
18	**1d**	 (**2j**)	94 (**21**)
19	**1d**	 (**2k**)	19 (**22**)
20	 (**1e**)	**2a**	27 (**23**)
21	 (**1f**)	**2a**	trace (**24**)
22	 (**1g**)	**2a**	trace (**25**)
23	 (**1h**)	**2a**	trace (**26**)

[a] Reaction conditions: **1** (0.25 mmol), **2** (2 equiv), $FeCl_3$ (10 mol %), **L1** (10 mol %), and K_2CO_3 (2 equiv) in THF (2 mL) at 90 °C for 22 h. [b] Isolated yield. [c] For 37 h.

Scheme 1. Possible Mechanism



arylboronic acids **2g** and **2h** provided low yields under the same conditions (entries 6 and 7). Next, a series of the other aryl aldehydes were investigated, and the results indicated that only electron-deficient aryl aldehydes were suitable substrates for the reaction (entries 8−22). Aryl aldehyde **1d** bearing two trifluoromethyl groups, for instance, underwent the 1,2-addition reaction with arylboronic acids **2a**, **2b**, **2e**, **2i**, or **2j**, $FeCl_3$, and **L1** smoothly in excellent yields (entries 14−18). However, the reaction between substrate **1d** and the electron-deficient arylboronic acid **2k** afforded the target product **22** in a low yield (entry 19). Unfortunately, the reactions of benzaldehyde (**1f**), 4-methoxybenzaldehyde (**1g**), or chalcone (**1h**) with phenylboronic acid (**2a**) were unsuccessful under the standard conditions (entries 21−23).

The electronic effect presented in the above results suggested that the present reaction underwent a nucleophilic attack process. Based on reported papers,[1−7] a working mechanism as outlined in Scheme 1 is proposed. First, complexation of $FeCl_3$ with ligand affords $FeCl_3L_n$. Subsequently, coordination of $FeCl_3L_n$ with aldehyde **1** readily occurs to afford intermediate **A**,[7c] followed by transmetalation of intermediate **A** with boronic acid **2** to generate an Ar′-Fe intermediate **B**. Insertion of C═O into the Fe−C bond in intermediate **B** then takes place to give intermediate **C**. Intermediate **C** undergoes hydrolysis with water to yield the target product and regenerate the active Fe catalyst.

In summary, we describe here the first example of 1,2-addition of aryl aldehydes with arylboronic acids using a $FeCl_3$ and 2-(di-*tert*-butylphosphino)biphenyl catalytic system. In the presence of $FeCl_3$ and 2-(di-*tert*-butylphosphino)biphenyl, a variety of electron-deficient aryl aldehydes were found to be suitable substrates for the reaction with arylboronic acids in moderate to excellent yields. It is noteworthy that the electronic effect of the functional groups both in arylaldehydes and arylboronic acids is found to play a crucial role in the present reaction. Work to probe the detailed mechanism and apply the Fe catalytic system in organic synthesis is currently underway.

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Supporting Information Available: Analytical data and spectra (^{1}H and ^{13}C NMR) for all the products, and typical procedure for $FeCl_3$-catalyzed addition of aryl aldehydes with arylboronic acids. This material is available free of charge via the Internet at http://pubs.acs.org.

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