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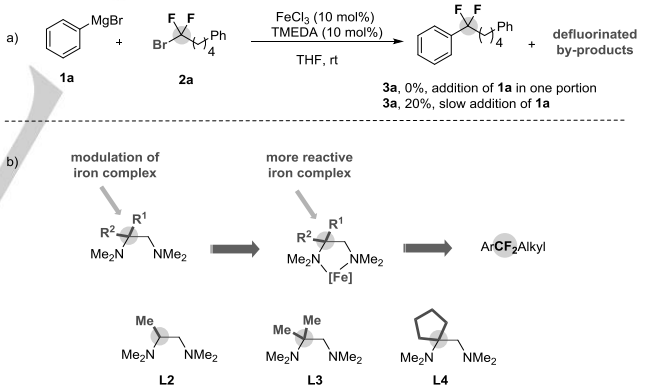
A Bulky Diamine Ligand Promoted Cross-Coupling with Difluoroalkyl Bromides via Iron Catalysis**

Lun An, Yu-Lan Xiao, Shu Zhang and Xingang Zhang*

Abstract: Although iron-catalyzed cross-coupling of Grignard reagents with alkyl halides has been well established, the adoption of the reaction for fluoroalkylations has not been reported because traditional catalytic systems often lead to defluorination reactions. Here, we describe our investigation of an iron-catalyzed cross-coupling between arylmagnesiums and difluoroalkyl bromides with steric modified *N*,*N*,*N*′,*N*′-tetramethyl-ethane-1,2-diamine (TMEDA) (**L4**) as a ligand. The use of a bulky diamine ligand (**L4**), in which a butylene is substituted at one carbon atom of ethylene backbone in TMEDA, enables the iron-catalyzed difluoroalkylation under mild reaction conditions with a wide range of difluoroalkyl bromides, including vulnerable bromodifluoromethane, thus providing a general and cost-efficient route for application in medicinal chemistry.

The demands of discovering new pharmaceuticals, agrochemicals and advanced functional materials have triggered extensive efforts on efficient synthesis of fluorinated compounds owing to the unique characteristics of fluorine atom(s) and C-F bond.[1] Over the past decade, the transition-metal catalyzed fluoroalkylations has emerged as an attractive and useful strategy to directly introduce fluorinated groups into organic molecules.[2] Most of these well developed methods are focused on copper-,[2, 3] palladium-[2, 4] and nickel-catalyzed fluoroalkylations,[2, 5] while the use of inexpensive, non-toxic and environmentally benign transition-metal, such as iron, as a catalyst remains appealing. For instance, although the iron catalyzed Kumada reactions have been well established since Kochi's pioneering work,[6, 7] the iron-catalyzed fluoroalkylations between Grignard reagents and fluoroalkyl halides has not been reported thus far because traditional catalytic systems often lead to defluorination reactions.[8] Herein, we report the first example of iron-catalyzed difluoroalkylation of arylmagnesiums with difluoroalkyl bromides. The approach allows a variety of difluoroalkyl bromides including gaseous bromodifluoromethane and provides a general and cost-efficient method to difluoroalkylated arenes, a distinct class of fluorinated compounds found in many biologically active molecules.[9]

Inspired by the previous work on iron/TMEDA (**L1**) catalyzed cross-coupling between Grignard reagents with alkyl halides,[10] initially, we focused our efforts on the cross-coupling of phenyl magnesium **1a** with unactivated difluoroalkyl bromide **2a** in the presence of $FeCl_3$ (10 mol%) with TMEDA (**L1**) (10 mol%) as a ligand (Scheme 1a). However, no desired difluoroalkylated arene **3a** was obtained due to the severe defluorination of **2a**. The slow addition of **1a** to the reaction system showed a beneficial effect, but only 20% yield of **3a** was obtained and the defluorination reactions remained to be a large hurdle. To address this crucial issue, a suitable iron-catalytic system is essential. We envisioned that if a diamine ligand could modulate the activity of iron center through its steric effect to facilitate the desired catalytic cycle, it would be feasible to realize such an iron-catalyzed difluoroalkylations.[11] Considering that the introduction of substituents on one carbon atom of ethylene backbone in TMEDA could influence the structure of iron complex thus altering its catalytic activity, we prepared three diamine ligands **L2**-**L4**[12] based on **L1**, and then synthesized their corresponding iron(II) complexes **A1-A4** (Scheme 1b and Figure 1) through the reaction of $FeCl_2$ with **L1-L4** individually in THF at room temperature, the similar conditions that was used in the subsequent cross-coupling reaction. To the best of our knowledge, investigation of these analogues of TMEDA on iron-catalyzed cross-couplings has never been reported thus far.



Scheme 1. Ligand design for iron-catalyzed cross-coupling of arylmagnesium bromide with difluoroalkyl bromide.

The single-crystal X-ray diffraction studies of **A1**-**A4**[13] showed that the iron complexes [{FeCl(TMEDA)}$_2$(u-Cl)$_2$] **A1** and [{FeCl(**L2**)}$_2$(u-Cl)$_2$] **A2** are the dinuclear complexes with two bridging chlorides, in which the two iron atoms are five coordinate. In contrast, the disubstituted diamine ligands **L3** and **L4** resulted in the mononuclear complexes [Fe(**L3**)Cl$_2$] **A3** and [Fe(**L4**)Cl$_2$] **A4**, in which the iron atom is four coordinate with pseudo-tetrahedral geometry, probably, because the introduction of steric interaction in **L3** and **L4** stabilizes the electron-deficient d^6 iron(II) species. The steric effect exemplifies in the increasing N-Fe-N angles in the order of [81.29(11)° ~ 81.45(9)°, **A1**] < [81.57(16)°, **A2**] < [82.65(5)°, **A3**] < [82.09(11)° ~ 82.81(10)°, **A4**].

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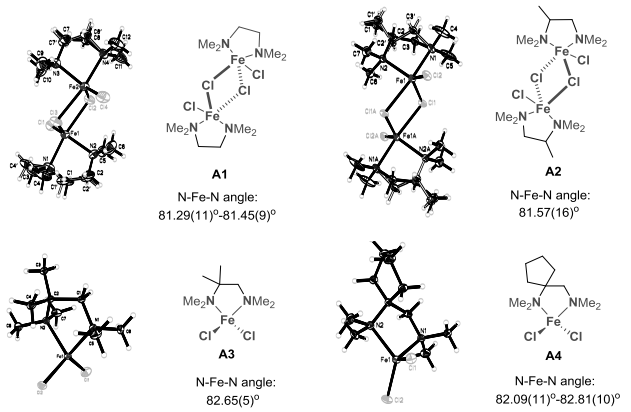
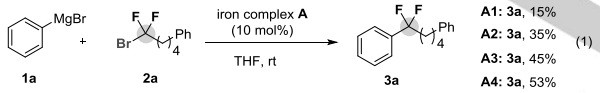


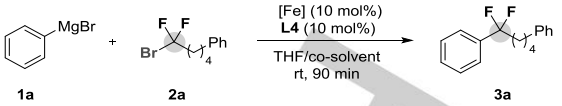
Figure 1. X-ray crystal structure of iron complexes **A1**-**A4**

Accordingly, the comparison of the catalytic activities of these iron complexes **A1**-**A4** was performed (eq 1). When the difluoroalkyl bromide **2a** was treated with arylmagnesium bromide **1a** in the presence of each of these iron complexes in THF at room temperature, the yields of **3a** were obtained in an increasing order **A1** (15%) < **A2** (35%) < **A3** (45%) < **A4** (53%). This order is in accordance with the order of N-Fe-N angle of iron complexes **A1**-**A4**, in which **A4** with the biggest N-Fe-N angle produced **3a** in the highest yield. Thus, these results suggest that the iron(II) complex chelating with a rigid diamine ligand with a relatively wide N-Fe-N angle benefits the catalytic cycle. It should be noted that in the iron-catalyzed Kumada cross-coupling of arylmagnesium bromide with cyclohexyl bromide, TMEDA ligand **L1** showed much better catalytic effect than much more rigid chelating amine ligands,[11d] indicating a different chemistry nature involved in the current iron-catalyzed difluoroalkylation. Probably, the steric hinderance in complex **A3** and **A4** that can slower the reaction of them with excessive Grignard reagent **1a** to form "ate" complexes[11d] are responsible for the better cross-coupling selectivity using ligand **L3** and **L4** than **L1** and **L2** in the model reaction.



Encouraged by these results, the diamine ligand **L4** was employed for further optimization of the reaction conditions (Table 1). It was found that the reaction was sensitive to the reaction medium (details see the Supporting Information, SI). The combination of dioxane with THF was prove to be the best reaction medium, providing **3a** in 82% yield (entry 2). The beneficial effect of dioxane is probably because dioxane shifts the Schlenk-equilibrium to Ar_2Mg. Switching $FeCl_2$ with $FeBr_2$ led to a slightly lower yield (80%) (entry 3). An optimal yield was achieved with FeI_2 as a catalyst (entry 4). **A1**-**A3** also furnished the desired product **3a**, but showed less activity (entries 5-7). The combinations of $FeCl_2$ with NaI or LiI to generate FeI_2 catalyst *in situ* were also examined, but comparable yields with the sole use of $FeCl_2$ as a catalyst was provided (SI). The absence of iron catalyst failed to provide **3a** and only defluorinated by-products were observed without **L4** (SI). Thus, these results demonstrate that the iron and diamine ligand **L4** plays an essential role in promotion of the reaction and the iron catalyst benefits defluorination of difluoroalkyl bromide in the absence of diamine ligand **L4**.

Table 1. Representative results for optimization of Fe-catalyzed difluoroalkylation of arylmagnesium bromide **1a** with difluoroalkyl bromide **2a**.[a]



Entry	[Fe]	Co-solvent	**3a**, Yield [%][b]
1	$FeCl_2$	none	40
2	$FeCl_2$	1,4-dioxane	82
3	$FeBr_2$	1,4-dioxane	80
4	FeI_2	1,4-dioxane	90 (88)
5[c]	**A1**	1,4-dioxane	33
6[c]	**A2**	1,4-dioxane	47
7[c]	**A3**	1,4-dioxane	65

[a] Reaction conditions (unless otherwise specified): **1a** (0.4 mmol, 2.0 equiv in 0.75 mL THF), **2a** (0.2 mmol, 1.0 equiv), THF (0.75 mL), co-solvent (0.25 mL). [b] Determined by ^{19}F NMR using fluorobenzene as an internal standard. [c] Reaction run in the absence of **L4**.

Upon the identification of viable reaction conditions, a variety of arylmagnesium bromides were employed for the current difluoroalkylations (Table 2). Overall, the electronic nature of arylmagnesium bromides did not interfere with the reaction efficiency and good to high yields of **3** were provided (**3a**-**3h**). Importantly, substrates bearing silyl group and 1,3-dioxolane moiety showed good tolerance to the reaction (**3i** and **3j**), thus offering opportunities for further transformations. The substrate scope of the reaction was not restricted to arylmagnesium bromides, a wide range of difluoroalkyl bromides were also suitable coupling partners (**3k**-**3v**). Many important functional groups, including silyl ether, sulfonate, ester, thiazole and ferrocenyl groups, were all compatible with the reaction conditions (**3k**-**3n**, **3p**, **3r**-**3t**), thus demonstrating the generality of current iron-catalyzed process. Furthermore, the difluoroalkylation of arylmagnesium bromide with intact a sulfonate group also exhibited the good chemoselectivity of the reaction (**3q**).[14] However, only 24-34% yields of the corresponding difluoroalkylated arenes were obtained when aryl chloride and bromide containing substrates were examined, due to the cross-coupling between arylmagnesium and aryl halides (**3u** and **3v**).

It has been documented that the difluoroethyl group (CF_2CH_3) can functionalize as a bioisostere of methoxyl group,[15] but limited methods to access difluoroethylated arenes have been reported so far.[15, 16] Accordingly, to demonstrate the generality of this method, 1-bromo-1,1-difluoroethane ($BrCF_2CH_3$) was also examined. As shown in Table 3, good to high yields of difluoroethylated arenes were still provided by using $FeBr_2$ as a catalyst (**5a**-**5d**), thus featuring the advantages of current process further. Most importantly, the reaction can also extend to bromodifluoromethane ($BrCF_2H$) **4b**. Usually, $BrCF_2H$ is sensitive to the basic conditions and prone to decomposition via a difluorocarbene pathway.[17] To date, no successful example of difluoromethylation of Grignard reagents with $BrCF_2H$ has been described. Nevertheless, the current iron-catalyzed process could enable difluoromethylation of a variety of arylmagnesium bromides with $BrCF_2H$ in good to high yields (**5e**-**5l**). In view of the important applications of difluoromethyalted arenes in medicinal chemistry,[18] this method would have potential applications in drug discovery and development.

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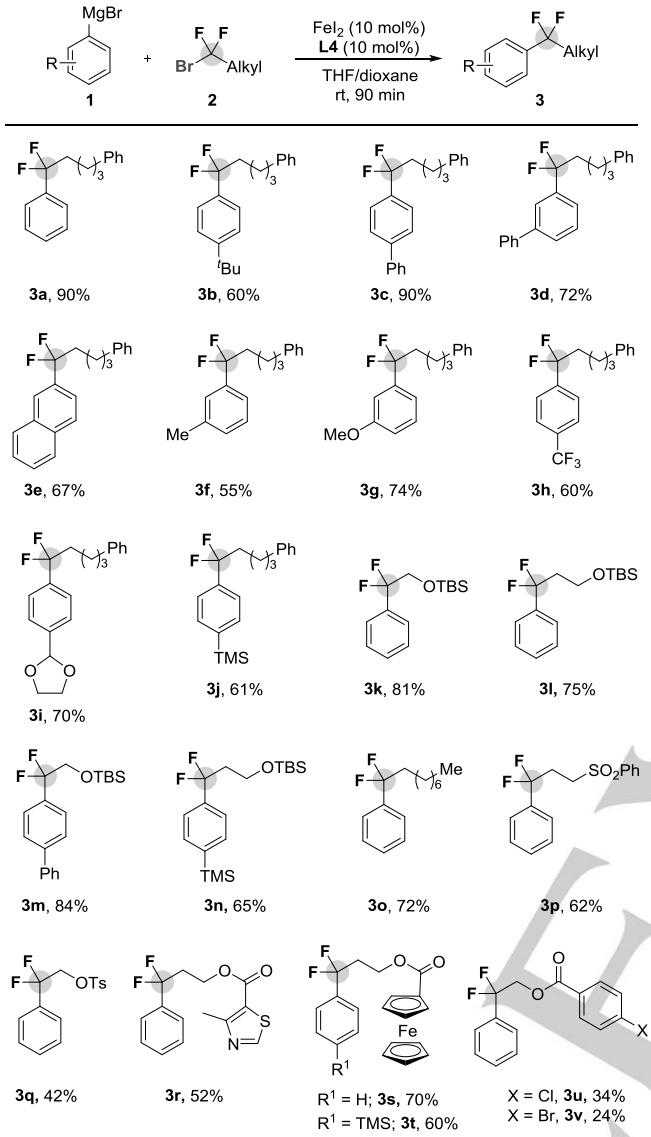
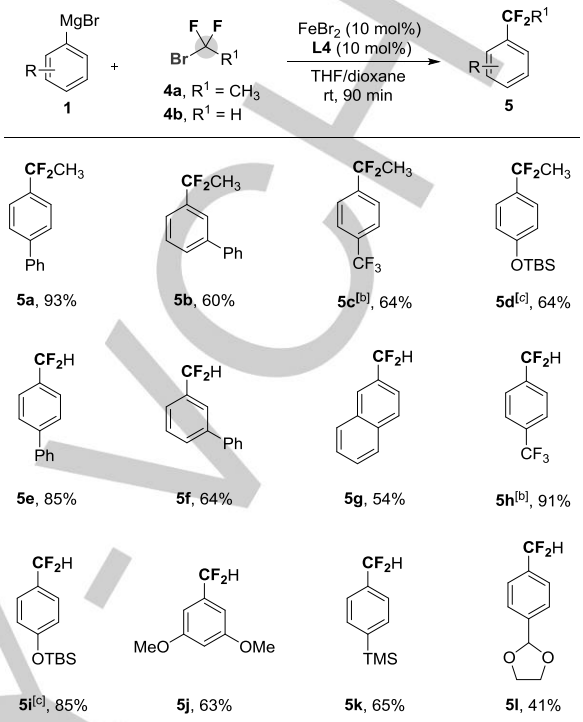
Table 2. Fe-catalyzed difluoroalkylations of arylmagnesium bromides **1** with difluoroalkyl bromides **2**.[a]



[a] Reaction conditions (unless otherwise specified): **1** (1 mmol, 2.0 equiv in 1.88 mL THF), **2** (0.5 mmol, 1.0 equiv), dioxane (0.63 mL) for 90 min.

In conclusion, we have demonstrated an iron/bulky diamine catalytic system that promotes the difluoroalkylation of arylmagnesium bromides with a wide range of difluoroalkyl bromides, including vulnerable $BrCF_2H$ under mild reaction conditions. This approach represents the first example of iron-catalyzed cross-coupling between Grignard reagents and fluoroalkyl halides. The deliberated substitution of TEMDA at its cabon backbone can significantly change the corresponding iron-complex from five coordinate (**A1**) to more electron dificient four coordinate (**A3** and **A4**), and thus improves the catalytic efficiency toward the cross-coupling difluoroalkylations and suppresses the side reactions of defluorination. To the best of knowledge, this is the first example of using **L4** as a ligand for organic synthesis.[12b] Because of its inexpensive and non-toxic iron catalyst as well as widely available Grignard reagents and difluoroalkyl bromides, this iron-catalyzed process provides a general and cost-efficient access to difluoroalkylated arenes that are of great interests in life and materials sciences. Most importantly, the beneficial effect of diamine ligand **L4** would also prompt research in iron-catalyzed cross-coupling. Further studies of using **L4** and its analogues on other reactions are now in progress in our laboratory.

Table 3. Fe-catalyzed difluoroethylation and difluoromethylation of arylmagnesium bromides **1**.[a]



[a] Reaction conditions (unless otherwise specified): **1** (1 mmol, 2.0 equiv in 1.88 mL THF), **4** (0.5 mmol, 1.0 equiv), dioxane (0.63 mL) for 90 min. All reported yields are isolated yields. [b] Determined by ^{19}F NMR using fluorobenzene as an internal standard. [c] 10 mol% of FeI_2 was used.

Acknowledgements ((optional))

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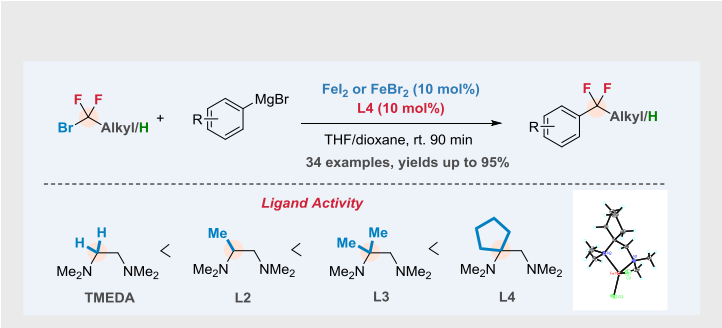

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Ligand design: A title reaction has been developed (see Scheme). The combination of iron(II) salts with a bulky diamine ligand **L4** enables the difluoroalkylations of arylmagnesium bromides with a wide range of difluoroalkyl bromides, providing a general and cost-efficient access to difluoroalkylated arenes that are of great interests in life and materials sciences.