Organic LETTERS

Letter

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Selective Alkylation and Arylation of C−F Bond with Grignard Reagents

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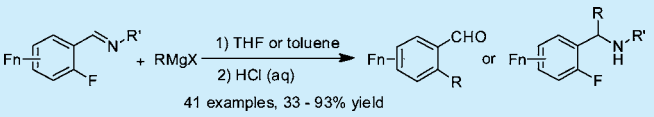
Supporting Information

ABSTRACT: Selective alkylation and arylation of the C−F bonds of polyfluoroaryl imines with Grignard reagents were discovered in the absence of metal catalysts. The aldazine-N atom as an anchoring group has a special effect on the regioselectivity of the reaction. The C═N bond addition reaction with Grignard reagents was also explored. A possible mechanism was proposed on the competition between the nucleophilic substitution and addition reaction.



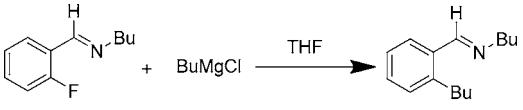
Fluorinated compounds are of considerable current interest in diverse fields of science and technology. More than 150 kinds of fluorinated drugs, nearly up to 20% of all pharmaceuticals, have come to market, and even 30% of agrochemicals contain fluorine atoms.[1]

Aromatic fluorides are the most widely used fluorinated compounds. Selective functionalization of C(sp^2)−F bonds has occupied an important position in the synthesis of aromatic fluorides. Transition-metal-catalyzed C−C bond-forming reactions are of great significance including Heck, Kumada, Sonogashira, Negishi, Stille, Suzuki, and Hiyama reactions. One approach to new aromatic fluorides is direct nucleophilic substitution of fluoroaromatics as a result of C−F bond activation and functionalization. However, the yields and selectivity are often low.[2,3]

In 1973, Kumada reported the first example of catalytic C−C cross-coupling of fluorobenzene with Grignard reagents by nickel catalysts.[4] In 2001, Herrmann reported that aryl fluorides reacted with aryl Grignard reagents affording a variety of biaryls using a nickel carbene complex.[5] In 2006, Radius disclosed the first examples of Ni-catalyzed C−C bond coupling between fluoroarenes and organoboron compounds.[6] Love reported another Ni-catalyzed Suzuki coupling in 2011. Organoboronic acids could react with the *ortho*-fluorine close to an aldazine-N atom in nearly quantitative conversion.[7] In 2012, Lu reported an example of *ortho*-(C−F) activation on palladium-catalyzed Suzuki−Miyaura reaction of polyfluorophenyl oxazoline.[8] Love reported a Pt-catalyzed C−F activation and functionalization with *ortho*-imine as directing group.[9] The similar catalysis could also be realized with nickel or cobalt complexes.[10] Weng published the synthesis of polyfluorinated aryl ethers via ligand-free palladium-catalyzed C−F activation of pentafluorobenzene with phenols.[11]

In addition, the early work with a directing group was done by Meyers.[12a] Cahiez described that $MnCl_2$ could significantly improve the yield of the nucleophilic substitution reaction of Grignard reagents with an aryl fluoride bearing an imino group in the *ortho*-position (Scheme 1).[12b] With heterocyclic group as anchoring group, C−F functionalization could also occurred.[12c] Morter summarized some examples in this field.[12d]

Scheme 1. Reaction with $MnCl_2$ as Catalyst

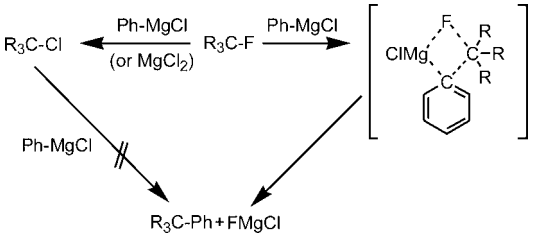


additive	conditions	yield
None	20°C, 24 h	40%
$MnCl_2$ (10 mol %)	20°C, 2 h	88%

While weak Lewis acidic magnesium reagents such as Grignard reagents are not believed to be able to activate strong C−F bonds, Koga explored the reaction without metal catalysts and proposed a possible mechanism involving a four-membered ring (Scheme 2).[13] Recently, Cao described nucleophilic substitution reaction of polyfluoroarenes with Grignard reagents via pyridine-directed cleavage of C−F bond.[14]

The transition-metal-free C−C bond formation was of great significance in practical applications. Particularly in the pharmaceutical industry, the demand for the absence of any transition metal impurity in final product was very strict. On the

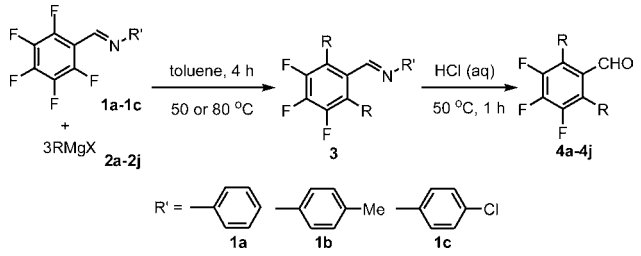
Scheme 2. Possible Mechanism of a Four-Membered Ring



Received: December 2, 2013
Published: January 16, 2014

   dx.doi.org/10.1021/ol403479r | *Org. Lett.* 2014, 16, 772−775

Table 1. *ortho*-Alkylation or Arylation of Perfluoroaryl Imines



entry	imine	RMgX	temp (°C)	product	yield[a,b] (%)
1	1a	2a	50	4a	95/85
2	1a	2b	50	4b	97/83
3	1b	2c	50	4c	95/87
4	1a	2d	50	4d	17/--
5	1c	2d	80	4d	98/88
6	1a	2e	50	4e	98/93
7	1b	2f	50	4f	95/89
8	1a	2g	80	4g	70/--
9	1b	2g	80	4g	98/92
10	1a	2h	80	4h	23/--
11	1b	2h	80	4h	56/--
12	1c	2h	80	4h	68/65
13	1b	2i	80	4i	51/--
14	1c	2i	80	4i	91/85
15	1b	2j	50	4j	95/90

[a]Yield of compound **3** was based on *in-situ* ^{19}F NMR spectra with (trifluoromethyl)benzene as an internal standard and was the average of 2 times [b]Isolated yields of **4**.

basis of the principle of green chemistry, we launched the research on synthesis approaches to aromatic fluorides without transition metal catalyst.

In this paper, we explored the functionalization of polyfluoroaryl imines with an aldazine-N atom as an anchoring group. We discovered that Grignard reagents could achieve nucleophilic substitution via C−F bond cleavage in high yield without metal catalysts with the excellent selectivity at the *ortho*-position close to the C═N bond. As far as we know, there has been no report on the imine-N atom-directed regioselectivity of this kind nucleophilic substitution in the range of C−F bond functionalization in the absence of metal catalysts.

The first investigation is the reaction of *N*-((perfluorophenyl)methylene)aniline (**1a**) with *n*-butyl MgBr (**2a**). Both of the two *ortho*-fluorine atoms were substituted by *n*-butyl within 4 h in 95% yield. After hydrolysis of **3**, 2,6-dibutyl-3,4,5-trifluorobenzaldehyde (**4a**) was obtained via column chromatography in 85% yield. To explore the reaction universality, we also studied the reactions of perfluoroaryl imines (**1b** and **1c**) with different Grignard reagents (**2b**−**2j**) (Table 1).

Nearly all of the studied aliphatic Grignard reagents have a desired yield in 50 °C except **2d** (entry 4). The aromatic Grignard reagents could not have an ideal result until the temperature rose to 80 °C. Comparing the results of entry 9 to 15, it was concluded that **1c** is the most active imine and **1b** is more active than **1a**. A heterocyclic Grignard reagent had similar activity with those of aliphatic and aromatic Grignard reagents (entry 15).

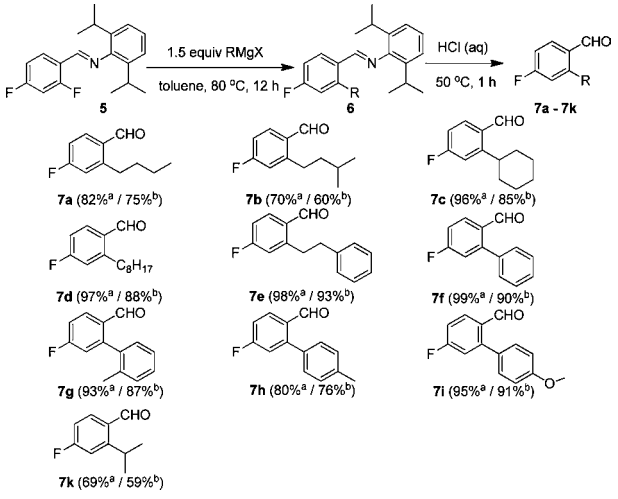
In addition to perfluoroaryl imines, we also explored the polyfluoroaryl imines with two or three C−F bonds. While we chose 2,4-difluoroaryl imines and 2,6-difluoroaryl imines as the substrates, it was very difficult for us to control the selectivity between the substitution of the *ortho*-F atom(s) and the addition of C═N bond. The selectivity could be improved by changing the steric hindrance. Compounds **5** and **8** were selected because both of them have isopropyl groups close to the C═N bond. The introduction of two *ortho*-isopropyl

dx.doi.org/10.1021/ol403479r | *Org. Lett.* 2014, 16, 772−775

groups protected the imine group from the nucleophilic attack of Grignard reagents.

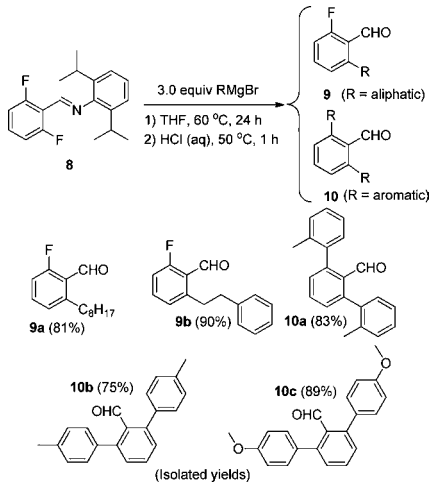
With the decreasing of number of F atoms on the aryl ring, the C−F bond activation became more difficult and the nucleophilic substitution needed longer time and higher temperature (Schemes 3 and 4).

Scheme 3. *ortho*-Alkylation or Arylation of 2,4-Difluoroaryl Imines



[a]Yields of **6** was based on *in-situ* ^{19}F NMR spectra with (trifluoromethyl)benzene as an internal standard and was the average of 2 times. [b]Isolated yields of **7**.

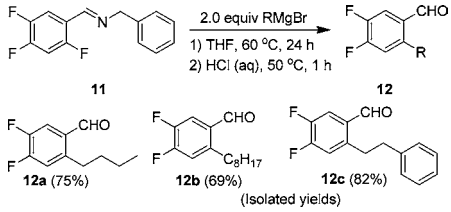
Scheme 4. *ortho*-Alkylation or Arylation of 2,6-Difluoroaryl Imines



It was noteworthy that the products of **8** with Grignard reagents could be monoalkylated or diphenylated (Scheme 4). It might be explained that the disubstitution product was formed from the monosubstitution product. The monophenylated intermediate to this nucleophilic substitution is more active than the monoalkylated products.

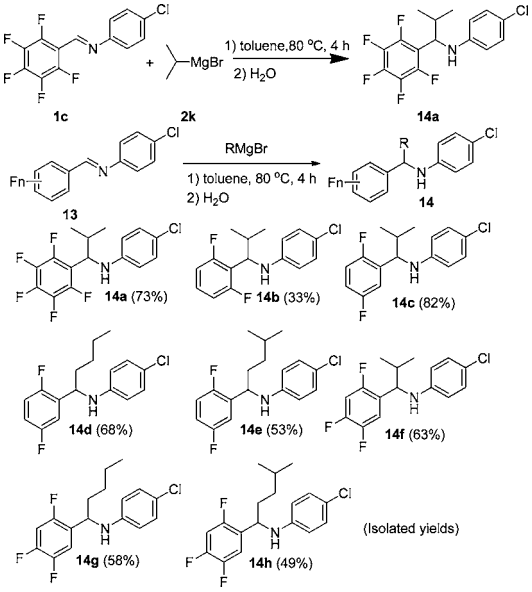
With trifluorinated imine **11** the monoalkylated products, aldehydes **12**, as *ortho*-(C−F) bond activation products were also isoalted in good yields (Scheme 5). This result is consistent with the imine-N atom-directed regioselectivity of C−F bond cleavage and C−C formation.

Scheme 5. *ortho*-Alkylation of 2,4,5-Trifluoroaryl Imine



The nucleophilic addition product **14a** was isloated from the reaction of **1c** with **2k** in the yield of 73%. It is obvious that the addition of C=N bond competed with the substitution reaction. More experimental results supported this opinion (Scheme 6). All the imines have a common feature. An

Scheme 6. Addition Reaction of C=N Bond

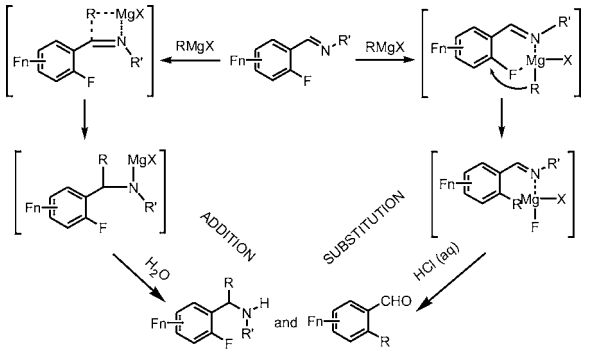


electron-withdrawing Cl atom is at the *para*-position in the phenyl ring, which links to the imine-N atom. This makes the imine-C atom more positively charged. In addition, no substituents at 2/6-position(s) are beneficial to the nucleophilic attack. However, the phenylated Grignard reagents could hardly react with the C=N bonds of the substrates under these conditions. This could be explained by their weak nucleophilicity and relatively larger steric hindrance.

On the basis of the experimental results and literature, a plausible mechanism was put forward on the regioselectivity of the nucleophilic substitution reaction in Scheme 7. The first step for the C−F bond functionalization should be the coordination of the N atom of the C=N bond to the magnesium center in the Grignard reagent. The interaction between the *ortho*-fluorine atom and the magnesium atom is beneficial to the attack of negatively charged alkyl group of the Grignard reagent on the *ortho*-carbon atom. Therefore, this six-membered chelate ring is formed by three C atoms, one N, one F, and one Mg atom. A new C−C bond is formed through the nucleophilic interaction between the R group and the electropositive carbon atom of the *ortho*-(C−F) bond. After hydrolysis, the imine transforms into the aldehyde (Path SUBSTITUTION).

dx.doi.org/10.1021/ol403479r | *Org. Lett.* 2014, 16, 772−775

Scheme 7. Proposed Mechanism



The nucleophilic addition of C═N bond with Grignard reagents proceeds via also the coordination of the imine-N atom to the Mg center (Path ADDITION). This mechanism is similar to that of the reaction between Grignard reagent and carbonyl compound. Electron-withdrawing groups on the imine-N-phenyl ring and the small steric hindrance are in favor of nucleophilic addition. The yields depend on the activity of both Grignard reagents and electrophiles.

The functionalization of the *ortho*-(C−F) bond of polyfluoroaryl imines with Grignard reagents competed with the addition of imine group. We consider that several factors, such as the number and the position of the F atoms, the property (aromatic or aliphatic of Grignard reagents, the steric effect of both substrates), play important role in this competition. In most of the cases we mainly obtained the substitution products in good to excellent yields, but we can not make use of the results of this paper to sum up the reaction rule. In some cases higher temperature is beneficial to the nucleophilic addition. For the excellent *ortho*-selectivity, the imine group must play a decisive role in the substitution.

In summary, we report an *ortho*-selective nucleophilic substitution of polyfluoroarenes with Grignard reagents via C−F bond activation to generate fluorinated benzaldehyde under mild conditions without transition metal catalyst. A possible mechanism is proposed. In general, the reactions have high yields, and the process is simply operated. This work is of great significance for C−F bond activation and functionalization of organic fluorides.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support of this work by NSFC (No.21172132) is gratefully acknowledged.

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