

A Facile Preparation of the Fluoroaryl Zinc Halides: an Application to the Synthesis of Diflunisal

Nakcheol Jeong,^{†,*} Sang Jo Lee, Ki Hang Choi, and Shin Chung

Hanhyo Institutes of Technology, 460-1 Chonmin-dong Yusong-gu, Taejeon 305-390, Korea

[†]Department of Chemistry, Korea University, 1 Anam-dong, Sungbuk-gu, Seoul 136-701, Korea

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Fluoroaryl moieties are often found in many pharmaceuticals such as non-steroidal antiinflammatory drugs, antifungal agents, and human antiparasitic agents.¹ And biphenyl skeletons have played key roles in several therapeutic areas and the most notable examples are AII - antagonists and salicylic acid derivatives. We have been interested in the preparation of diflunisal **1**,² an important analgesics and anti-inflammatory agent and devised the strategy including direct cross coupling between arylmetallics and a fully functionalized aryl halide.

Cross coupling reactions of the organometallics with a variety of organic electrophiles using transition metals³ have provided useful methods for C-C bond formation. Employment of the highly reactive organometallic precursors in the coupling reaction often precluded the presence of the labile functional groups on the reacting substrates. Thus the preparation of such molecules with high degree of functionality requires the protection-deprotection steps as well as the functional group interconversion afterward. The recent advances employing organometallics with milder reactivity, such as organotin,⁴ boron⁵ and zinc reagents,⁶ in the coupling reaction allow the expansion of the scope of the reactions and to have direct accesses to the molecules, which were difficult to obtain previously.

Despite such progress, the narrow scope of the functional group compatibility of organometallics, attributed to the intrinsic problems in the preparation of such reagents, still need to be overcome for the broader applications. Since the most commonly used methods for new organometallics are transmetalation from organolithiums or Grignard reagents with other metal salts, only a few functional groups are compatible with these methods. Recently, direct preparation of the organoboron and tin reagents mediated by transition metals from the corresponding halides or triflates has been devised to obtain the functionalized organometallic reagents.

Meantime, the direct zinc insertion into aryl iodide reported

by Knochel has provided a way to get the functionalized organozinc reagents.^{6b} The insertion of zinc into aryl iodides bearing electron-withdrawing substituents in polar solvents such as DMF and DMAC smoothly proceeded to give the corresponding arylzinc halides in excellent yield. Moreover zinc is cheap and safe and it can be a choice for practical process. Thus, we decided to test this method for the direct synthesis of diflunisal (**1**).

First, we examined the direct insertion of zinc into aryl iodide **2-a**. We soon realized that the direct insertion of zinc into **2-a** was not practical. A reduced product, 2-acetoxy methylbenzoate (**4-b**) instead of **4-a** was obtained as a major product even under carefully controlled inert condition. Later, we switched the strategy and found that the insertion of zinc into 2,4-difluorophenyl iodide (**3-a**) was accomplished in high efficiency (Scheme 2).⁷ This process was so efficient that the reaction took place within only 15 min in DMF even at ambient temperature. This dramatic rate acceleration in zinc insertion is unusual and remarkable for fluoroaryl compounds. Even commercially available zinc dust (1.2-5 eq) could be used after brief activation with dibromoethane.

Furthermore, a projected complication such as benzyne formation from *o*-fluoro iodobenzene was not observed during the process, and it might be due to the high covalency of the zinc-carbon bond. Zinc insertion into the fluoroaryl bromides was possible although the reaction was rather sluggish. But aryl chlorides remained inert even at the elevated reaction temperature. Regardless of substitution pattern, fluoroaryl iodide afforded the corresponding zinc complexes nicely. Even pentafluoroaryl iodide turned out to be one of the best substrates in this metal insertion.

Subsequent coupling of the resulting arylzinc reagents with the functionalized aryl iodides by palladium (0) catalysts (usually less than 5%) was successfully carried out. The reaction mixture was treated by either heating at 50 °C

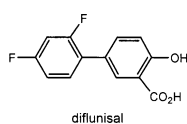


Figure 1

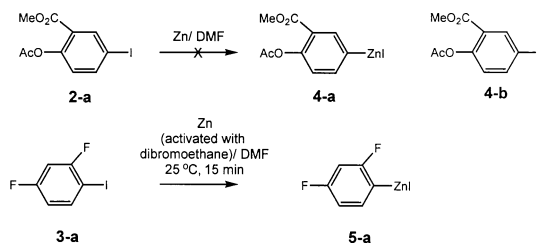
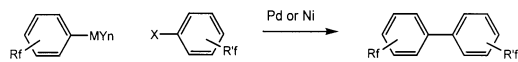


Table 1. Representative Examples of the Preparation of the Fluorinated Biphenyls

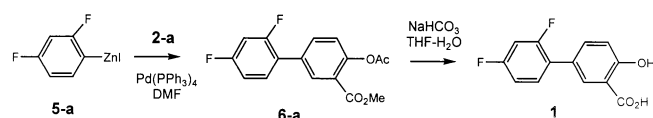
Entry	Fluoroarylzinc halide	Aryl halides	Products ^a	Yield ^b
1				90%
2				97%
3				74%
4				85%
5				94%
6				82%
7				93%
8				95%
9				96%
10				83%

^aAll products showed satisfactory spectroscopic data. ^bChemical yields given were obtained for the two step operations and based on the aryl iodide (2). They were determined after chromatographic separation.

for 1-2 hr or stirring at rt for 10-24 hr. The fluorobiphenyls (**6**) were obtained in high yields. And two step reactions could be carried out in one-pot operation. The yields were determined based on the limiting substrates, aryl halides (**2**) (0.9eq of theoretical amount of the corresponding metal species).

The scope and the functional group compatibility of the reaction are summarized in Table 1. Any electrophilic aryl halides listed in the Table can be used as good counterparts of the fluoroarylzinc halides. Esters, ketones and even free amines (entry 5 and 6) are tolerable in the coupling reaction.

In a practical application, the coupling between **3-a** and **2-a** proceeded to give **4-a** even at rt in almost quantitative yield (97% yield based on **2-a**).⁸ Usual hydrolysis of **4** with sodium bicarbonate afforded diflunisal (**1**) in 95% yield (Scheme 3). This result provided a far superior process to the originally proposed Merck process or newly introduced

**Scheme 3**

Zambon process. According to the patent, the former included Gomberg reaction of difluorophenyl diazonium salt with benzene to construct the biphenyl skeleton. And the latter used the coupling between 2,4-difluoroaryl halides and 4-methoxyphenylzinc halide in the presence of palladium (0). The resulting coupling product (2,4-difluorophenyl) benzene had to be functionalized in four more steps to give **1**.

In conclusion, we have demonstrated the facile preparations of the fluoroaryl zinc iodides by direct insertion of zinc into fluoroaryliodides and their coupling with the highly functionalized arylhalides to yield the fluorinated biphenyls in high yield by the aid of palladium (0) catalysts.

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8. A typical procedure:

To a suspension of zinc dust (0.408 g, 6.24 mmol) in anhydrous DMF (3 mL) was added 1,2-dibromoethane (53 mL, 0.624 mmol). The mixture was warmed at 50 °C for 10 min. After the mixture was cooled to rt, 2,4-difluoro-1-iodobenzene (0.500 g, 2.08 mmol) was added and the resultant mixture was allowed to react at rt for 15 min. 5-Iodosalicylate (**2-a**) (0.630 g, 1.97 mmol) and tetrakis-(triphenylphosphine)palladium (0.114 g) was introduced to the mixture and the mixture was stirred at rt for 2 hr. The reaction mixture was filtered through Celite and extracted with ethyl acetate and water. The organic layer was dried over anhydrous MgSO₄ and concentrated. The residue was chromatographed (SiO₂, hexane/ethyl acetate = 4 : 1) to give (**6-a**) (0.618 g, 1.91 mmol, 97%).