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Palladium-Catalyzed Negishi Cross-Coupling Reaction of Aryl Halides with (Difluoromethyl)zinc Reagent

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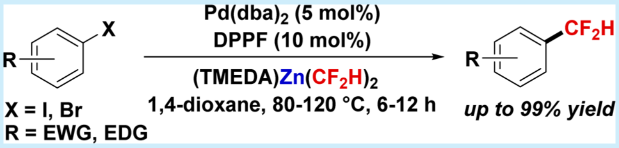
S Supporting Information

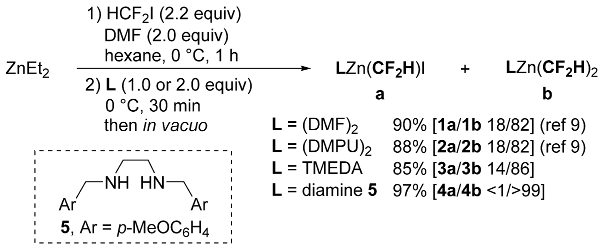


ABSTRACT: The palladium-catalyzed Negishi cross-coupling reaction of aryl iodides and bromides with (difluoromethyl)zinc reagent bearing a diamine such as TMEDA is achieved to provide the difluoromethylated aromatic compounds in good to excellent yields. The advantages of (difluoromethyl)zinc reagent are that (1) the derivatives, which possess different stability and reactivity, can be readily prepared via ligand screening and (2) transmetalation of a difluoromethyl group from the zinc reagent to palladium catalyst efficiently proceeds without an activator.

Recently, interest in aromatic compounds bearing a difluoromethyl (−CF$_2$H) group, which can be regarded as a bioisostere of alcohols and thiols, has grown in the pharmaceutical and agrochemical industries.[1] As part of a direct and regiospecific synthetic method for difluoromethylated aromatic compounds, Hartwig and Prakash independently disclosed the copper-mediated difluoromethylations of aryl iodides with TMSCF$_2$H and nBu$_3$SnCF$_2$H as difluoromethyl sources.[2,3] However, to the best our knowledge, the catalytic difluoromethylation of aryl halides with difluoromethyl reagents is still conspicuously limited, in sharp contrast to the corresponding synthetic methods for the CF$_3$[4] and CF$_2$R[5] groups.[6] In 2014, the first catalytic difluoromethylation of aryl halides with TMSCF$_2$H was demonstrated by Shen using the cooperative dual palladium/silver catalyst system.[7] Moreover, Vicic succeeded in the nickel-catalyzed difluoromethylation of aryl halides by employment of (DMPU)$_2$Zn(CF$_2$H)$_2$.[8] In the preceding paper, we reported the copper-catalyzed difluoromethylation of aryl iodides with (DMPU)$_2$Zn(CF$_2$H)$_2$ as an organozinc reagent.[9] The reaction proceeded efficiently through the ligand/activator-free operation, providing the difluoromethylated aromatic compounds in moderate to high yields. However, the fundamental drawback of the reaction is that only aryl iodides bearing electron-withdrawing substituents can be utilized, and thus, aryl iodides possessing electron-donating substituents are not applicable. Herein, we report the palladium-catalyzed Negishi cross-coupling reaction with a (difluoromethyl)zinc reagent that occurs with aryl halides bearing not only electron-withdrawing substituents but also electron-donating substituents.[10]

We have previously provided synthetic protocols involving (trifluoromethyl)-,[11,12] (perfluoroalkyl)-,[11,12d,13] and (difluoromethyl)zinc[8,9,14] reagents. The advantage of these zinc reagents is that derivatives possessing different stability and reactivity depending on the ligands can be readily prepared through the screening. Therefore, we sought to investigate (difluoromethyl) zinc reagents bearing not only monodentate ligands such as DMF and DMPU but also diamine ligands (Scheme 1). We found that the preparation of (DMF)$_2$Zn(CF$_2$H)$_2$ (**1b**) and (DMF)$_2$Zn(CF$_2$H)I (**1a**) (82:18) according to the previous procedure[9] followed by the ligand exchange between DMF and diamines, such as TMEDA and diamine **5**, could produce the corresponding zinc reagents, LZn(CF$_2$H)$_2$ (**3b** and **4b**) in high yields as major products, respectively. The structure of **4b** was defined by X-ray crystallography as having tetrahedral geometry at zinc (Figure 1).[15,16] With regard to the stability of zinc reagents in DMF solution, we found that diamine ligands can thermally stabilize the zinc reagents. In fact, although (TMEDA)Zn(CF$_2$H)$_2$ almost decomposed at 60 °C after 24 h, the decomposition rate was slower than that of counterparts bearing monodentate ligands. Moreover, LZn(CF$_2$H)$_2$ (L = **5**) was more stable at 60 °C, and 51% of the zinc reagent remained even after 24 h.[15]

Scheme 1. Preparation of (Difluoromethyl)zinc Reagents[a]



[a] Yield and ratio of **a**/**b** were determined by ^{19}F NMR spectroscopy.

Next, transmetalation of the CF$_2$H group to palladium from zinc was examined by ^{19}F NMR spectroscopy (Table 1). The addition of (DMPU)$_2$Zn(CF$_2$H)$_2$ to (DPPF)Pd(Ph)I (**6**) proceeded smoothly at room temperature to afford (DPPF)-

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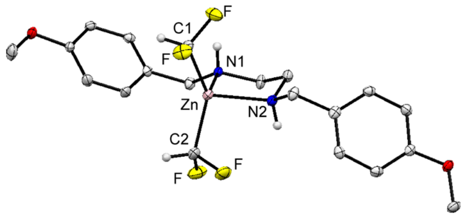
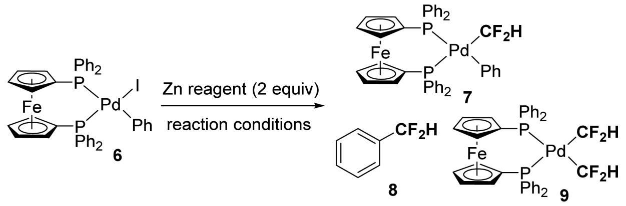


Figure 1. X-ray structure of **4b**. Selected hydrogen atoms are shown. Angles: C1−Zn−C2, 132.41°; N1−Zn−N2, 83.09°. Bond lengths: C1−Zn, 2.028 Å; C2−Zn, 2.031 Å; N1−Zn, 2.140 Å; N2−Zn, 2.133 Å.

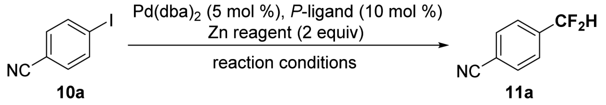
Table 1. Transmetalation of CF_2H Group



entry	Zn reagent[a]	reaction conditions	yield[b] (%) of [7/8/9]
1	$(DMF)_2Zn(CF_2H)_2$	1,4-dioxane, rt, 1 h	49/0/11
2	$(DMPU)_2Zn(CF_2H)_2$	1,4-dioxane, rt, 1 h	94/0/1
3	$(TMEDA)Zn(CF_2H)_2$	1,4-dioxane, 50 °C, 1 h	22/8/0 (0/91/0)[c]
4	$(\mathbf{5})Zn(CF_2H)_2$	1,4-dioxane, rt, 1 h	93/0/3
5	$(DMF)_2Zn(CF_2H)I$	1,4-dioxane, rt to 100 °C, 12 h	0/0/0[d]

[a] $LZn(CF_2H)_2$ and $(DMF)_2Zn(CF_2H)I$ prepared according to the methods shown in Scheme and our previous report (ref 9) were employed, respectively. [b] Yield was determined by ^{19}F NMR spectroscopy. [c] Reaction time was 24 h. [d] $(DPPF)Pd(CF_2H)I$ was observed in 20−40% yields.

Table 2. Catalytic Difluoromethylation of Aryl Iodide[a]



entry	Zn reagent[b]	P-ligand	reaction conditions	yield[c] (%)
1	$(DMF)_2Zn(CF_2H)I$	DPPF	1,4-dioxane, 80 °C, 12 h	5
2	$(DMF)_2Zn(CF_2H)_2$	DPPF	1,4-dioxane, 80 °C, 12 h	35
3	$(DMPU)_2Zn(CF_2H)_2$	DPPF	1,4-dioxane, 80 °C, 12 h	57
4	**$(TMEDA)Zn(CF_2H)_2$**	**DPPF**	**1,4-dioxane, 80 °C, 12 h**	**73**
5	$(\mathbf{5})Zn(CF_2H)_2$	DPPF	1,4-dioxane, 80 °C, 12 h	58
6	$(TMEDA)Zn(CF_2H)_2$	DPPF	toluene, 80 °C, 12 h	71
7	$(TMEDA)Zn(CF_2H)_2$	DPPF	DMF, 80 °C, 12 h	65
8	$(TMEDA)Zn(CF_2H)_2$	DPPF	THF, 80 °C, 12 h	67
9	$(TMEDA)Zn(CF_2H)_2$	DPPF	1,4-dioxane, 100 °C, 6 h	76
10	**$(TMEDA)Zn(CF_2H)_2$**	**DPPF**	**1,4-dioxane, 120 °C, 6 h**	**81** (74)[d]
11	$(TMEDA)Zn(CF_2H)_2$	DPPE	1,4-dioxane, 120 °C, 6 h	11
12	$(TMEDA)Zn(CF_2H)_2$	DPPP	1,4-dioxane, 120 °C, 6 h	17
13	$(TMEDA)Zn(CF_2H)_2$	BINAP	1,4-dioxane, 120 °C, 6 h	51
14	$(TMEDA)Zn(CF_2H)_2$	$P(1\text{-}Ad)_2n\text{Bu}$	1,4-dioxane, 120 °C, 6 h	15

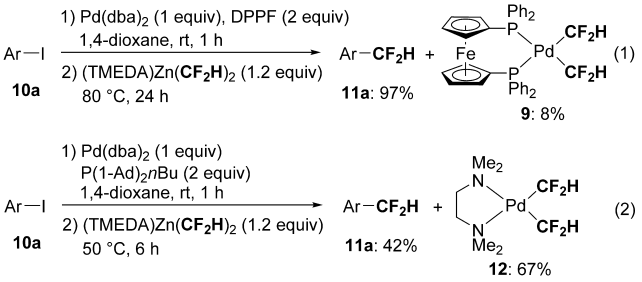
[a] Conditions: **10a** (0.1 mmol), zinc reagent (~0.5 M 1,4-dioxane solution: 0.2 mmol), $Pd(dba)_2$ (5 mol %), and *P*-ligand (10 mol %). [b] $LZn(CF_2H)_2$ and $(DMF)_2Zn(CF_2H)I$ prepared according to the methods shown in Scheme 1 and our previous report (ref 9) were employed, respectively. [c] Yield was determined by ^{19}F NMR spectroscopy. [d] Reaction time was 3 h.

$Pd(Ph)(CF_2H)$ (**7**) in 94% yield. The use of $(DMF)_2Zn(CF_2H)_2$, in contrast, resulted in the formation of **7** and $(DPPF)Pd(CF_2H)_2$ (**9**) in 49% and 11% yields, respectively (Table 1, entries 1 vs 2). Complex **9** was found to be catalytically inactive. Transmetalation of **6** using $(TMEDA)Zn(CF_2H)_2$ required higher temperature (Table 1, entry 3) and provided (difluoromethyl)benzene (**8**) in addition to **7** (entry 3). Indeed, Shen has already reported that complex **7** can undergo reductive elimination at 47 °C, providing **8** in high yield.[7a] In contrast, $LZn(CF_2H)_2$ (**L** = **5**) bearing diamine efficiently underwent transmetalation even at room temperature (entry 4). To our surprise, $(DMF)_2Zn(CF_2H)I$ did not cause the desirable transmetalation even at 100 °C, and $(DPPF)Pd(CF_2H)I$ was observed in 20−40% yields at the same time as decomposition of the zinc reagent in the ^{19}F NMR spectrum (entry 5).

With preparation of (difluoromethyl)zinc reagents and observation of the transmetalation, our research was focused on the catalytic difluoromethylation of aryl halides (Table 2). We tested various zinc reagents, phosphine ligands, solvents, and reaction temperature. Initially, the reactions were conducted with 4-iodobenzonitrile (**10a**) and $(DMF)_2Zn(CF_2H)I$ or $(DMF)_2Zn(CF_2H)_2$ in the presence of $Pd(dba)_2$/2DPPF in 1,4-dioxane at 80 °C to provide the desired product (**11a**), but yields were low (entries 1 and 2). Although $(DMPU)_2Zn(CF_2H)_2$ gave moderate yield under the same conditions (entry 3), we were delighted to find that use of $(TMEDA)Zn(CF_2H)_2$ could lead to **11a** in 73% yield (entry 4). However, $\mathbf{L}Zn(CF_2H)_2$ (**L** = **5**) decreased the yield (entry 5). Other solvents, such as toluene, DMF, and THF, also initiated the reaction but did not enhance the yields (entries 6−8). Higher temperature (120 °C) led to higher yield (entry 10), while the reaction proceeded smoothly even at 80 °C (entry 4). Bidentate ligands, such as DPPE, DPPP, and BINAP, led to a significant drop in yields (entries 10 vs 11−13). No improvement of yields was observed even by bulky monodentate ligand (entry 14).

The nature of the phosphine ligands had a large impact on the yields of the reactions. For example, the stoichiometric examination of $Pd(dba)_2$/2DPPF and **10a** in the presence of $(TMEDA)Zn(CF_2H)_2$ could provide the difluoromethylated product (**11a**) in 97% yield, along with a slight amount of $(DPPF)Pd(CF_2H)_2$ (**9**) (Scheme 2, eq 1). In sharp contrast, employment of bulky monodentate ligand $P(1\text{-}Ad)n\text{Bu}_2$ also furnished **11a** in 42% yield. In this case, however, $(TMEDA)Pd(CF_2H)_2$ (**12**) was provided as a major product (67% yield) in a ligand-exchange reaction and was found to be inactive in the catalytic cycle (Scheme 2, eq 2). These results indicate that relatively electron-donating bidentate ligands, which can suppress the production of the inert complex **12**, are suitable for the present catalytic system.

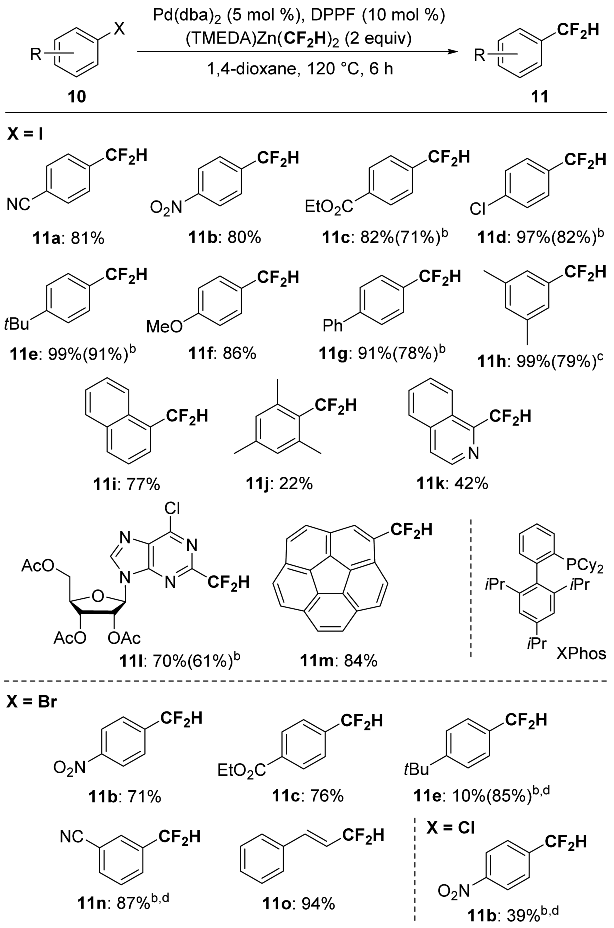
Scheme 2. Stoichiometric Examination[a]



[a]Yield was determined by ^{19}F NMR spectroscopy. (TMEDA)Zn(CF_2H)$_2$ prepared according to the method shown in Scheme 1 was employed.

Scheme 3 summarizes the scope of the aromatic difluoromethylation with various aryl and heteroaryl iodides and bromides under the reaction conditions optimized in Table 2. In general, aryl iodides possessing electron-withdrawing substituents in the *para*-position of the ring, such as nitro, ester, and chloride, were found to undergo the difluoromethylation in good to high yields (**11b–d**). Significantly, substrates bearing electron-donating substituents and a phenyl group also reacted smoothly to give the desired products **11e–g** in high yields. In addition, the reaction employing *meta*- and *ortho*-substituted aryl iodides could be converted to the difluoromethylated arenes (**11h,i**), but *ortho*-disubstituted arene and isoquinoline led to diminished reactivity (**11j,k**). Purine riboside was compatible with the present catalytic reaction (**11l**). The introduction of the CF_2H group was also found to be applicable to corannulene backbone (**11m**). Aryl bromides with electron-withdrawing substituents in the *para*-position underwent the reaction to afford the products **11b,c** in good yields. Furthermore, by using XPhos instead of DPPF, the reaction of aryl bromides bearing electron-donating and withdrawing substituents in the *para*- and *meta*-positions resulted in the formation of the products **11e,n** in high yields, respectively. Vinylic substrate was also compatible with the present reaction (**11o**). The reaction of aryl chloride with an electron-withdrawing substituent occurred to give the corresponding product (**11b**), albeit in 39% yield.

Scheme 3. Substrate Scope and Functional-Group Tolerance[a]



[a]Conditions: **10** (0.3 mmol), (TMEDA)Zn(CF_2H)$_2$ (~0.5 M 1,4-dioxane solution: 0.6 mmol), Pd(dba)$_2$ (5 mol %), and DPPF (10 mol %) in 1,4-dioxane (2 mL). Yield was determined by ^{19}F NMR spectroscopy. (TMEDA)Zn(CF_2H)$_2$ prepared according to the method shown in Scheme 1 was employed. [b]Reaction was carried out at 80 °C for 12 h. [c]Pd(dba)$_2$ (2 mol %) and DPPF (4 mol %) were used. [d]XPhos instead of DPPF was used.

In summary, an efficient and practical palladium-catalyzed Negishi cross-coupling reaction of aryl iodides and bromides was developed with (TMEDA)Zn(CF_2H)$_2$ as an organozinc reagent. Transmetalation of the CF_2H group from zinc reagents to palladium catalyst proceeded efficiently without an activator, in contrast to the counterparts employing TMSCF$_2$H and nBu$_3$SnCF$_2$H as difluoromethyl sources.[2,3,7] This difluoromethylation protocol was carried out with aryl iodides and bromides bearing not only electron-withdrawing but also electron-donating substituents, affording the difluoromethylated arenes in good to excellent yields. To demonstrate the efficiency and versatility of a palladium catalytic system which can be easily optimized depending on substrates, development of the palladium-catalyzed difluoromethylations with various (hetero)aryl bromides, triflates, and chlorides with (difluoromethyl)zinc reagents is now underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01734.

Experimental procedures and compound characterization data (PDF)

X-ray crystallographic data for **4b** (CIF)

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Notes

The authors declare no competing financial interest.

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