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# Cobalt/diamine-catalyzed 1,1-difluoroethylation and 2,2,2-trifluoroethylation of aryl Grignard reagents with corresponding fluoroalkyl halides

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ABSTRACT

Cobalt/diamine-catalyzed 1,1-difluoroethylation and 2,2,2-trifluoroethylation of aryl Grignard reagents with 1,1-difluoroethyl and 2,2,2-trifluoroethyl halides were investigated. With regard to the 1,1-difluoroethylation, 1,2-bis(dimethylamino)-2-methylpropane, which has been rarely used in the cross-coupling reactions, gave the highest yield among the diamine ligands tested. In the 2,2,2-trifluoroethylation, *trans*-1,2-bis(dimethylamino)cyclohexane provided the desired products in satisfactory yields with not only 2,2,2-trifluoroethyl iodide but also chloride. This Co/diamine catalyst was also effective for the coupling with other partially fluorinated alkyl halides in the presence of appropriate diamine ligands.



## 1. Introduction

Because trifluoromethyl and difluoromethyl groups directly bound to aromatic rings give unique bio-active character, numerous syntheses of aromatic compounds containing these functional groups have been reported [1,2]. In a similar manner, other fluoroalkyl groups, particularly partially fluorinated alkyl groups, have received much attention for medical and agricultural compounds [3]. Recently, the remarkable bioactivity of heteroaromatic compounds and nucleobases featuring the 1,1-difluoroethyl ($CH_3CF_2$) group, which mimics the steric and electronic features of methoxy group [4b–e], has been explored [4]. Thus far, aromatic compounds having $CH_3CF_2$ group have been synthesized *via* fluorination of functional groups on aromatic rings with various fluorinating reagents. Fluorination of the ethynyl group in phenylacetylene using HF-organic base provides 1,1-difluoroethylbenzene [5]. Deoxo-fluor (bis(2-methoxyethyl)aminosulfur trifluoride) [6] or phenylsulfur chlorotetrafluoride [7] converts the acetyl group in acetophenone to $CH_3CF_2$ group, yielding 1,1-difluoroethylbenzene. Similarly, 3-acetylindoles were converted to 3-(1,1-difluoroethyl)indoles with DAST (*N,N*-diethylaminosulfur trifluoride) [8]. The use of Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) [9] or uranium hexafluoride [10] gives 1,1-difluoroethylbenzenes from 2-methyl-2-phenyl-1,3-dithiolane or 2-aryl-1,3-dithianes. The methylene hydrogen atoms in ethylbenzenes can be selectively substituted with fluorine atoms by using Selectfluor or Selectfluor II (4-fluoro-1-methyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) in the presence of a catalytic amount of xanthone [11][11a] or $Na_2S_2O_8$ [11b,c]. Very recently, fluorination of (1-chloroethenyl) benzene or 1-bromo-4-(1-chloroethenyl)benzene with HF to (1,1-difluoroethyl)benzene or 1-bromo-4-(1,1-difluoroethyl)benzene, respectively, was reported in a patent [12]. This method appears to be more practical than the other ones, because HF is the most inexpensive fluorinating reagent.

On the other hand, 1,1-difluoroethylation of aromatic compounds via cross-coupling using 1,1-difluoroethyl halides [13] or their metal reagents has not been reported to the best of our knowledge, although it requires no toxic and expensive fluorination reagents. In particular, the cross-coupling of 1,1-difluoroethyl halides and arylmetal reagents can be a practical and usable process because of its availability of substrates.

With regard to 2,2,2-trifluoroethylation, which furnishes bioactive aromatic compounds possessing the 2,2,2-trifluoroethyl ($CF_3CH_2$) group [14], several examples of palladium-catalyzed cross-couplings of 2,2,2-trifluoroethyl iodide or triflate and arylboronic acids or their esters have been reported [15]. However, they require a large amount of palladium, expensive ligands such as 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl and optionally CuCl. Xu et al. reported the Cu-promoted coupling of aryliodides 2,2,2-trifluoroethyl iodide [16]. Although this reaction proceeds without any ligands and bases, the excess amount of Cu

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powder and the long reaction time, 55 h, are necessary. Recently, Ackermann et al. showed 2,2,2-trifluoroethylation with $CF_3CH_2I$ through C—H bond activation with a catalyst consisting of [(dimethoxyethane)$NiCl_2$] and bis(2-dimethylaminoethyl) ether [17], though the substrates of this reaction were limited to benzamides and 2,2,2-trifluoroethylation occurred only at the *ortho* position of an amide group. In addition, the radical 2,2,2-trifluoroethylation of aromatic C—H bond with zinc (2,2,2-trifluoroethyl)sulphinate afforded only 15% yields [18].

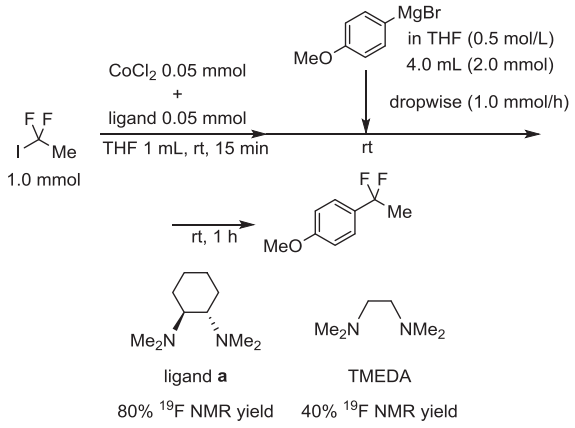
We began our investigation with the aim of realizing a more general and practical cross-coupling process for partially fluorinated alkylation. Therefore, we focused on a catalyst consisting of cobalt and a diamine ligand that catalyzes the cross-coupling of aryl Grignard reagents and alkyl halides [19] or arylzinc reagents and ethyl bromodifluoroacetate [20]. As a result, we found that 1,1-difluoroethylation and 2,2,2-trifluoroethylation proceeded smoothly with readily available 1,1-difluoroethyl iodide ($CH_3CF_2I$), 1,1-difluoroethyl bromide ($CH_3CF_2Br$) or 2,2,2-trifluoroethyl iodide ($CF_3CH_2I$) and aryl Grignard reagents in the presence of a Co/diamine catalyst. Interestingly, 2,2,2-trifluoroethylation also occurred by the use of corresponding chloride ($CF_3CH_2Cl$), which should be rather inactive. Based on the other partially fluorinated alkylation by the use of partially fluorinated alkyl halides possessing three or four carbons, we revealed that the yields largely depended on the diamine ligand.

## 2. Results and discussion

### 2.1. 1,1-Difluoroethylation

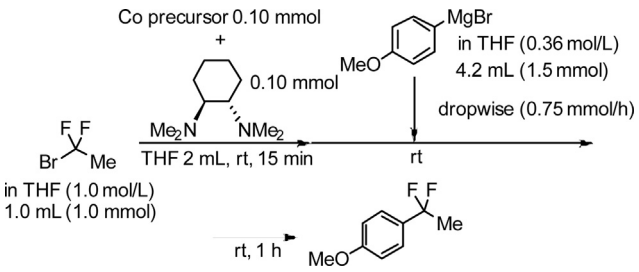
Scheme 1 illustrates the reaction of 4-methoxyphenyl Grignard reagent and $CH_3CF_2I$ with $CoCl_2$ as a cobalt precursor and *trans*-1,2-bis(dimethylamino) cyclohexane (ligand **a**) or *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) as a diamine ligand; these diamine ligands were used in the previously reported cobalt-catalyzed cross-coupling [19,20]. The desired product was obtained in 40% and 80% $^{19}F$ NMR yield, respectively. This result indicated that the cobalt/diamine catalyst could be used for the target reaction and that surveying the reaction conditions to obtain the higher yields was worthwhile.

First, the reaction with 4-methoxyphenyl Grignard reagent was examined with various cobalt precursors and diamine ligands. $CH_3CF_2Br$ was used in this examination instead of the iodide, because (i) it is less expensive than the iodide, and (ii) the differences derived from the precursors and ligands could be clearer owing to its lower reactivity compared to the iodide. Taking into account the low boiling point (14 °C) of $CH_3CF_2Br$, the




**Scheme 1.** Cobalt/diamine catalyzed coupling of $CH_3CF_2I$ and 4-methoxyphenyl Grignard reagent.

**Table 1**
Cobalt/diamine-catalyzed coupling of $CH_3CF_2Br$ and 4-methoxyphenyl Grignard reagent with various Co precursors.




| entry | Co precursor | yield/%[a] |
|---|---|---|
| 1 | $CoCl_2$ | 62 |
| 2 | $CoBr_2$ | 67 |
| 3 | $CoI_2$ | 79 |
| 4 | $CoF_2$ | 2 |
| 5 | $CoF_3$ | 3 |
| 6 | $Co(OAc)_2$ | 55 |
| 7 | $Co(acac)_2$ | 58 |
| 8 | $Co(acac)_3$ | 40 |
| 9[b] | $CoCl_2$ | 52 |
| 10[b] | $CoBr_2$ | 54 |
| 11[b] | $CoI_2$ | 74 |

[a] Determined by $^{19}F$ NMR.
[b] Co precursor 0.05 mmol, ligand 0.05 mmol.

reactions were carried out with a THF solution of the bromide. Table 1 lists the results obtained using various cobalt precursors with ligand **a** that gave the higher yield in Scheme 1. As anticipated from the reactivity of the bromide, the yield with $CoCl_2$ decreased to 62%, which was lower than that with the bromide, 80% (entry 1). Of the cobalt halides tested, $CoI_2$ provided the highest yield of the desired product (entry 3). Both divalent and trivalent fluoride salts were inactive (entries 4 and 5). A divalent acetate precursor gave a moderate yield (entry 6). With regard to acetylacetonate precursors, both divalent and trivalent precursors provided moderate yields (entries 7 and 8). When 0.05 mmol of $CoI_2$, $CoBr_2$ or $CoCl_2$ and ligand **a** were used, all the yields decreased (entries 9–11) and a satisfactory yield, 74%, was obtained only with $CoI_2$. Based on the results in Table 1, 0.10 mmol of $CoCl_2$ was chosen as the precursor hereinafter, because it gave a satisfactory yield and was readily available.

Fig. 1 shows the $^{19}F$ NMR yields of 1-(1,1-difluoroethyl)-4-methoxybenzene from $CH_3CF_2Br$ and 4-methoxyphenyl Grignard reagent with $CoCl_2$ and various diamines featuring an *N,N,N′,N′*-tetramethylethylenediamine backbone as a ligand. Although the yield with ligand **a** was larger than that with TMEDA, each ligand afforded a lower yield than Scheme 1. This is readily anticipated by the lower reactivity of bromide than iodide. Interestingly, only 1,2-bis(dimethylamino)-2-methylpropane (ligand **b**) gave a higher yield than ligand **a** (89% vs. 62%) among the diamines tested. This compound is known as a catalyst in polyurethane synthesis [21] and is one of the ligands in $LiNEt_2$-catalyzed hydroamination [22]. However, it has never been used in cross-coupling reactions to the best of our knowledge. All of the other diamine ligands also afforded lower yields than ligand **a** and **b**. In addition, bis(2-dimethylaminoethyl) ether, which was used in the nickel-catalyzed 2,2,2-trifluoroethylation through C—H bond activation afforded no desired product at all.

Based on the results in Table 1 and Fig. 1, we chose ligand **a** (*trans*-1,2-bis(dimethylamino) cyclohexane), which has been used previously in the cobalt-catalyzed cross-coupling, and ligand **b** (1,2-bis(dimethylamino)-2-methylpropane), which revealed its