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Synthesis of trifluoromethylated compounds from alcohols via alkoxydiphenylphosphines

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ABSTRACT

The transformation of hydroxyl group in benzyl or allyl alcohols to trifluoromethyl was achieved via the reaction of the corresponding alkyloxydiphenylphosphine and $CuCF_3$, generated *in situ* from methyl fluorosulfonyldifluoroacetate and CuI, under mild conditions. A plausible mechanism was proposed on the basis of experimental results.

1. Introduction

Recently, organofluorine chemistry has been developed greatly and played a significant role in a wide range of applications [1]. Among various fluorine-containing compounds, trifluoromethylated compounds received more and more attention due to their unique physical, physiological, and pharmacokinetic properties. Accordingly, considerable efforts have been made to introduce trifluoromethyl group selectively and directly [2]. So far many effective methods have been developed, for example, the transformation of methyl group to trifluoromethyl group by chlorination and the following fluorination with hydrogen fluoride or metal fluoride [3]. In late 1980s, an efficient trifluoromethylation strategy involving trifluoromethyl copper ($CuCF_3$) intermediate formed *in situ* from methyl fluorosulfonyldifluoroacetate and copper iodide (CuI) was developed by Chen and coworkers, and has been extensively applied in academic and industrial fields [4]. More recently, trifluoromethyl copper as a trifluoromethylation reagent was extensively investigated due to its high efficiency [5].

Similarly, many methods have been developed for the synthesis of (trifluoroethyl)arenes. The direct transition metal-mediated trifluoroethylation of arylboronic acids [6] and trifluoromethylation of benzyl halides [7] via the $Cu\text{-}CF_3$ species generated from different precursors are convenient ones. Copper-mediated trifluoromethylation of allylic chlorides and trifluoroacetates was also achieved by using a $Cu\text{-}CF_3$ reagent. These reactions are suitable for selective synthesis of allyl trifluoromethyl species. Although these methods are proven efficient, it is still highly desirable to develop new protocols for their synthesis.

The hydroxyl group is one of the most common functional groups in organic molecules. If it can be transformed to trifluoromethyl group, various trifluoromethylated compounds would be conveniently obtained [8]. In 2013, Szabó and coworkers reported the trifluoromethylation of allylic chlorides and trifluoroacetates using a convenient $Cu\text{-}CF_3$ reagent [9a]. Qing et al. also reported the Cu-mediated trifluoromethylation of benzyl methanesulfonates [9b]. On the other hand, Mukaiyama and coworkers developed an oxidation–reduction condensation reaction which is known as one of the most useful synthetic methods in organic synthesis [10]. Various esters, ethers, nitriles and sulfides can be prepared from alcohols in excellent yields under mild conditions by the combined use of alkoxydiphenylphosphines and quinones [11]. In 2003, the one-pot cross-coupling reaction of alkoxymethyldiphenylphosphonium iodides and Grignard reagents in the presence of iodomethane was reported (Scheme 1) [12]. In the reaction, an ionic intermediate (**A**) was firstly formed and reacted with Grignard reagents to give the corresponding cross-coupling product along with $Ph_2MeP{=}O$ and MgXI.

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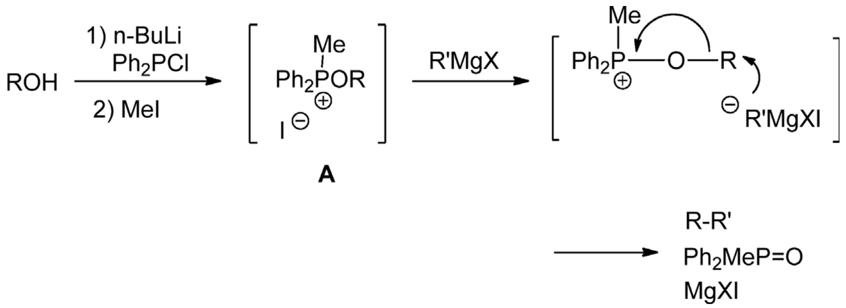
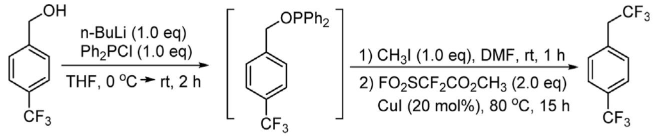


Scheme 1. The cross-coupling reaction of alkoxymethyldiphenylphosphonium iodides and Grignard reagents.



1a **2a** **3a**, 32%

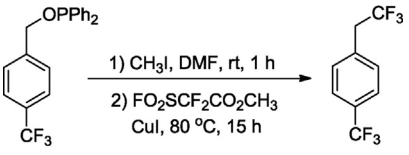
Scheme 2. The trifluoromethylation reaction of 4-trifluormethylbenzyl alcohol.

Inspired by above-mentioned reactions, we envisioned that intermediate **A** might react with the $CuCF_3$ species formed *in situ* from methyl fluorosulfonyldifluoroacetate and CuI in a similar way to afford trifluoromethyl compounds and phosphine oxide. Herein, we report the realization of a mild method to transform the hydroxyl group in benzyl or allyl alcohols to trifluoromethyl via alkyloxydiphenylphosphines.

2. Results and discussion

According to literatures [10,11], 4-trifluoromethylbenzyloxydiphenylphosphine (**2a**) was easily prepared by the reaction of 4-trifluoromethylbenzyl alcohol (**1a**) with *n*-BuLi and the subsequent reaction with Ph_2PCl in tetrahydrofuran (THF). Initially, phosphinite **2a** was treated with 1.0 equiv of methyl iodide in dimethylformide (DMF) at room temperature. After 1 h, 2.0 equiv of methyl fluorosulfonyldifluoroacetate and 20 mol% of copper iodide were added and the mixture was stirred at 80 °C. Full conversion of **2a** was achieved in 15 h, and gratifyingly the desired product 1-(2,2,2-trifluoroethyl)-4-(trifluoromethyl)benzene (**3a**) was obtained in 32% yield (Scheme 2).

Table 1
Optimization of reaction conditions.



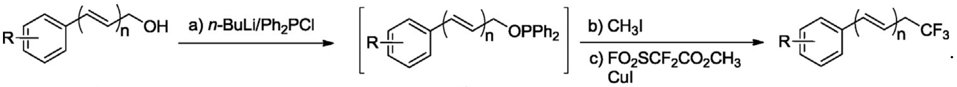
2a **3a**

Entry[a]	CH_3I (equiv)	$FO_2SCF_2CO_2CH_3$ (equiv)	CuI (equiv)	DMF (mL)	Yield[b] (%)
1	1	2	0.2	3	32
2	2	2	0.2	3	38
3	3	2	0.2	3	42
4	3	2	0.1	3	35
5	3	2	0.3	3	40
6	3	2	0.2	6	65
7	3	3	0.2	6	70
8	3	4	0.2	6	72

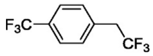
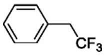
[a] Reaction conditions: (1) **2a** (1.5 mmol), CH_3I, DMF, rt, 1 h; (2) $FO_2SCF_2CO_2CH_3$, CuI, 80 °C, 15 h.
[b] Isolated yields.

Optimization of the reaction conditions was then carried out and the results were shown in Table 1. Increasing the amount of methyl iodide to 3.0 equiv, the yield of **3a** was improved to 42% (Table 1, entries 1–3). Changing catalyst loading had little influence on the reaction (entries 4–5). Considering the low solubility of CuI in DMF, more DMF was tried and it was found that when the amount of DMF was increased from 3.0 to 6.0 mL, the yield of **3a**

Table 2
The reaction of substituted benzyl alcohols and allyl alochols with trifluoromethylating reagent.



1, n = 0~1 **2** **3**

Entry[a]	**1** (R, *n*)	Product **3**	Yield (%)[b]
1	**1a** (*p*-CF_3, 0)	 **3a**	70
2	**1b** (H, 0)	 **3b**	70