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A Stereoselective Synthesis of γ,δ-Unsaturated Ketones Possessing Perfluoroalkyl Groups by Trifluoroborane Etherate Mediated 1,4-Addition Reaction of Alkenyldiisopropoxyboranes to α,β-Unsaturated Ketones

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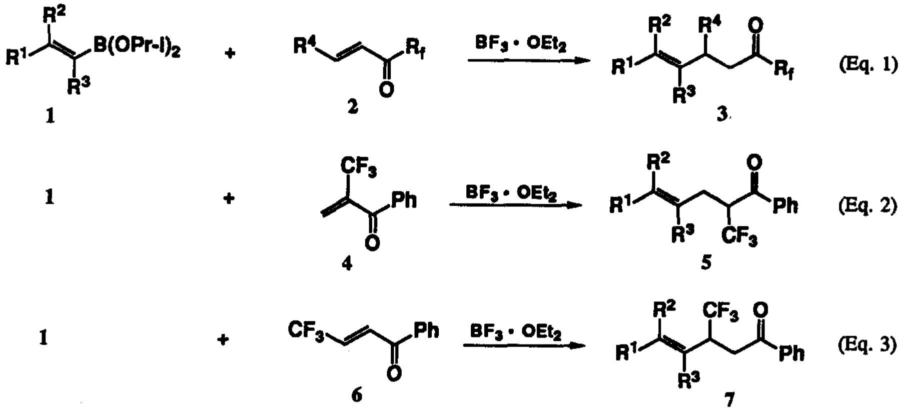
Abstract: A variety of γ,δ-unsaturated ketones (3,5, and 7) having perfluoroalkyl groups were prepared stereoselectively by the trifluoroborane etherate mediated 1,4-addition reaction of alkenyldiisopropoxyboranes (1) to α,β–unsaturated ketones substituted by perfluoroalkyl group (2,4, and 6). The undesired 1,2-addition of alkenyl groups or elimination of metal fluoride from the adducts could be avoided completely and the products were obtained in good yields.

Fluorinated compounds have been of great interest to synthetic and medical chemists due to the unique physical and biological properties imparted by fluorine.[1] Among them, fluorinated ketones are the subject of renewed interest by organic chemists, because of their roles as synthons in the preparation of more complex molecules as well as their own biological properties as enzyme inhibitors.[2]

1,4-Addition reaction of organometallic compounds to fluorinated α,β-unsaturated ketones is an effective method for the synthesis of fluorinated ketones having the desired structure. However, the strong electron-withdrawing character[3] and the lability[5] of fluoroalkyl group attached to the unsaturated ketones restrict their application for the reaction with organometallic compounds, such as organocopper reagents. Especially, the stereoselective synthesis of γ,δ-unsaturated ketones having perfluoroalkyl groups by the 1,4-addition reaction of alkenyl metals to the corresponding α,β-unsaturated ketones has never been reported.[6]

Recently, we reported that alkenyldialkoxyboranes react with α,β-unsaturated ketones in the presence of trifluoroborane etherate to give γ,δ-unsaturated ketones stereoselectively.[9] During the course of the study, we have found that the trifluoroborane etherate mediated 1,4-addition of alkenyldialkoxyboranes is applicable for the reaction with unsaturated ketones substituted by perfluoroalkyl groups, which gives the corresponding γ,δ-unsaturated ketones in good yields with high stereoselectivity (Eqs 1, 2, and 3).

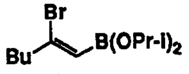
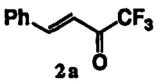
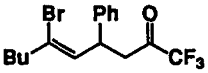
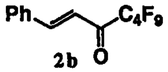
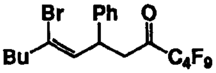
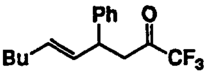
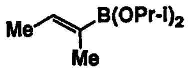
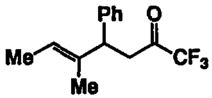
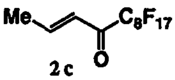
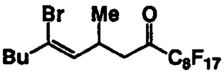
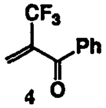
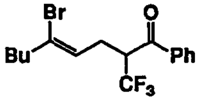
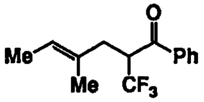
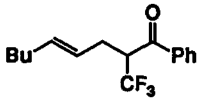
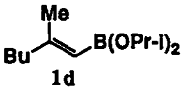
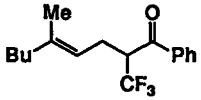
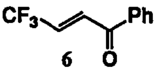
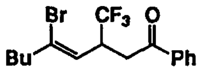
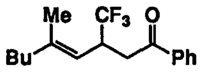


In the presence of trifluoroborane etherate, α,β-unsaturated ketones with perfluoroalkyl groups on the carbonyl carbon (**2a, b, and c**)[10] were found to react with a variety of alkenyldiisopropoxyboranes (**1a, b,** and **c**) to give the corresponding γ,δ-unsaturated ketones (**3**) in good yields without the formation of 1,2-addition products. The good results were also obtained from α-(trifluoromethyl)vinyl phenyl ketone (**4**).[11] In the reaction of organocopper reagents with α,β-unsaturated carbonyl compounds having fluorine at the β-position of carbonyl group such as **4**, the fast elimination of metal fluoride from the 1,4-addition intermediates always prevents the formation of desired fluorinated products.[5] However, such an elimination reaction did not occur at all in the reaction of alkenyldiisopropoxyboranes (**1a, b, c,** and **d**) and the desired trifluoromethyl substituted products (**5**) were obtained in good yields. On the other hand, β-(trifluoromethyl)vinyl phenyl ketone (**6**)[14] showed relatively low reactivity towards **1** under the reaction conditions and the 1,4-addition products could be obtained only from **1a** and **1b** in reasonable yields (Table 1).

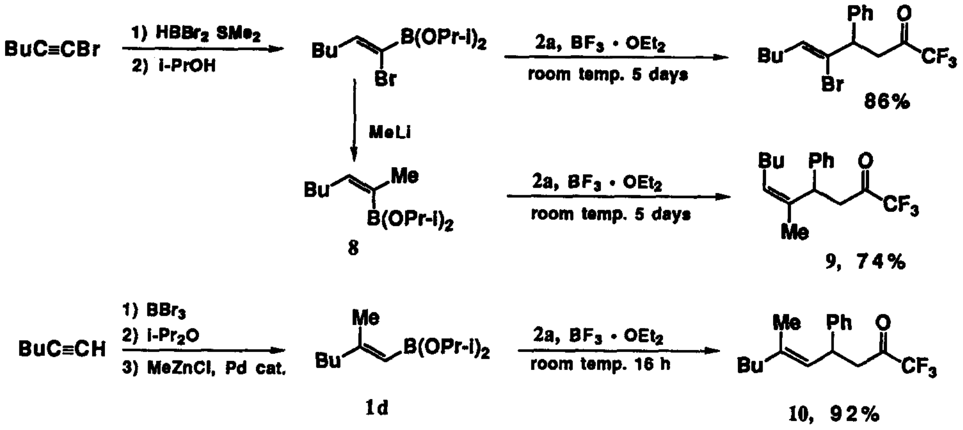
The application of **1** for the synthesis of fluorinated γ,δ-unsaturated ketones has the clear advantage over the use of other organometallic compounds. By using hydroboration reaction or haloboration reaction of alkynes, 1,2- or 2,2-disubstituted alkenyldiisopropoxyboranes as well as (E)- and (Z)-monosubstituted alkenylborane derivatives can be prepared stereoselectively, and they can be used for the 1,4-addition reaction. For instance, (E)-(1-methyl-1-hexenyl)diisopropoxyborane (**8**),[16] prepared from 1-bromo-1-hexyne by hydroboration and methylation, reacted with **2a** to give (Z)-3-methyl-2-phenyl-3-octenyl trifluoromethyl ketone (**9**) stereoselectively. From (E)-(2-methyl-1-hexenyl)diisopropoxyborane (**1d**),[9] (E)-4-methyl-2-phenyl-3-octenyl trifluoromethyl ketone (**10**) was obtained stereoselectively as shown in scheme 1.

The following procedure for the synthesis of (Z)-4-bromo-2-phenyl-3-octenyl trifluoromethyl ketone is representative. To a mixture of **1a** (582 mg, 2 mmol) and **2a** (200 mg, 1 mmol) in dichloromethane (10 ml) was added at room temperature trifluoroborane etherate (0.246 ml, 2 mmol), and the mixture was stirred under reflux overnight. The complete consumption of **2a** was confirmed by glpc analysis. The product was extracted with ether and the organic layer was washed with aqueous sodium hydrogen carbonate and then water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The purification of the product by column chromatography (silica gel / hexane : dichloromethane = 4 : 1) gave 358 mg of 1,4-addition product (99 % yield).

Table 1. Synthesis of γ,δ-Unsaturated Ketones Possessing Perfluoroalkyl Groups

Entry	Borane	Enone	React. cond.	Product[a]	Yield, %[b]
1	 1a	 2a	40 °C, 12h		99
2	1a	 2b	40 °C, 12h		91
3	 1b	2a	room temp. 6 days		82
4	 1c	2a	room temp. 12 h		88
5	1a	 2c	40 °C 2 days		79
6	1a	 4	room temp. 24h		85
7	1c	4	room temp. 19h		83
8	1b	4	room temp. 4 days		76
9	 1d	4	room temp. 4 days		83
10	1a	 6	room temp. 4 days		81
11	1d	6	room temp. 2 days		77

a. Isomeric purity of double bond is more than 95 %.
b. Isolated yield based on ketone used.



Scheme 1

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