

Convenient Synthesis of α,α -Difluorinated Carbonyl Compounds from Alkynes through a Fluoro-deboronation Process

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Abstract: Catalytic diboration of alkynes towards alkenyl diboronates provides suitable intermediates that can be converted into α -fluorinated and α,α -difluorinated carbonyl compounds via electrophilic fluorination with Selectfluor.

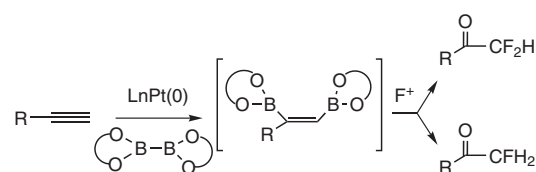
Key words: alkynes, alkenyl diboronates, electrophilic fluorination, Selectfluor, α,α -difluoroketones

Organoboron compounds are considered useful intermediates in organic synthesis.^{1,2} Transition metal complexes play an important role in the borylation of unsaturated substrates, but only Pt(0) complexes efficiently catalyze the introduction of two boryl units, at a time, into an alkyne.^{3–5} Clean addition of tetraalkoxy- and tetraaryl-oxydiboranes, (RO)₂B–B(OR)₂, to terminal and internal alkynes in the presence of Pt(PPh₃)₄ was first described in 1993 by Ishiyama et al., where isomerically pure *cis*-1,2-bis(boryl)alkenes were produced.⁶ The success of this catalytic transformation could be related to easy oxidative addition of the diboranes on the low-valent transition metal complexes,^{7–9} and to the inhibited β -hydride elimination within the alkenyl borane intermediates throughout the catalytic cycle.¹⁰ The number of phosphine ligands bound to platinum in the catalytic system seems to play a significant role.^{8,9,11} Even the phosphine-free platinum complexes proved to be active in the catalytic diboration of alkynes.¹²

One interesting transformation of the *cis*-1,2-bis(boryl)alkenes involves the palladium-catalyzed cross-coupling reaction with aryl, alkenyl, benzyl, and allyl halides to allow di- and monosubstitution to occur selectively influenced by the nature of the base.^{6,13} However, to the best of our knowledge, no other reaction has been described that can transform the boryl units into interesting functional groups, such as fluorines. In view of the unique features of fluorine-containing compounds,¹⁴ there has been increasing interest in the development of novel and practical synthetic methods for preparing fluorinated molecules.¹⁵

Herein, we report a new method for synthesizing α -fluorinated and α,α -difluorinated carbonyl compounds from alkynes in a sequential reaction, including platinum(0)-catalyzed diboration followed by electrophilic fluoro-de-

boration workup (Scheme 1). The novelty of this process is that two new functional groups (carbonyl and fluorides) are regioselectively formed through the boron chemistry.



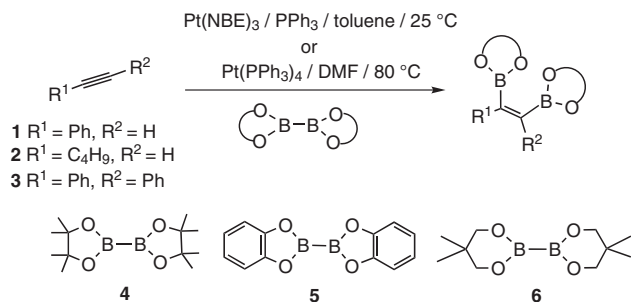
Scheme 1

The introduction of fluorine atoms adjacent to the carbonyl functionality increases the electrophilicity of the carbonyl carbon atom and consequently facilitates the addition of nucleophiles. It is worth mentioning that it has been suggested that the nucleophilic addition of enzyme active sites to the carbonyl group of α -fluoroketones is responsible for the inhibition of a variety of enzymes.¹⁶ α -Fluoroketones have been synthesized so far from well established routes: fluoride ion displacement of a halide from α -halocarbonyls,¹⁶ the reaction of diazo derivatives with HF,¹⁶ and electrophilic fluorinations of enolates.^{17,18} However, in all these synthetic routes the carbonyl functional group had already been formed.

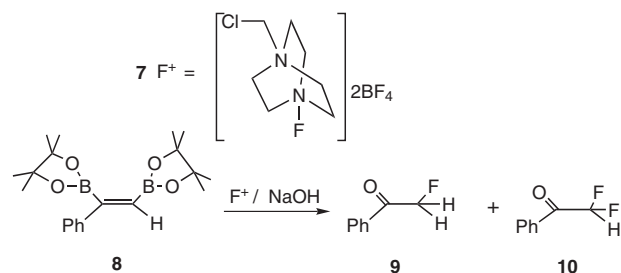
In this context we first tried to isolate stereodefined *cis*-1,2-bis(boryl)alkenes from the addition of diboron reagents to internal and terminal alkynes, **1–3**, in presence of Pt(0) complexes. Tetraalkoxydiboranes, such as bis(pinacolato)diboron (**4**), bis(catecholato)diboron (**5**) and bis(neopentylglycolato)diboron (**6**), were chosen to be added to the alkynes. However, following the methodologies described previously in the literature,^{7,11} we were only able to isolate the *cis*-1,2-bis(boryl)alkenes quantitatively when diboron **4** reagent was used.

Next, we explored the possibility of performing electrophilic fluorination on the alkenyl diboronates, in the presence of commercially available electrophilic reagents such as 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate (**7**, Selectfluor)¹⁹ (Scheme 3).

cis-1,2-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)styrene (**8**) was cleanly and selectively fluorinated at the terminal boryl unit. The addition of one equivalent of Selectfluor (**7**) to a solution of the alkenyl diboronate **8** in acetonitrile at room temperature provided a quasi equal



Scheme 2



Scheme 3

mixture of the α -fluorinated and α,α -difluorinated carbonyl compounds (Figure 1). The addition of two and three equivalents of the electrophilic fluorinated reagent favored the formation of the α,α -difluorinated carbonyl derivative with yields of up to 95% (Figure 1). This is of particular importance because we found in the literature that 2,2-difluoro derivatives could only be obtained by electrophilic fluorination of very reactive β -dicarbonyl compounds under neutral conditions via their metal enolates.^{20–23}

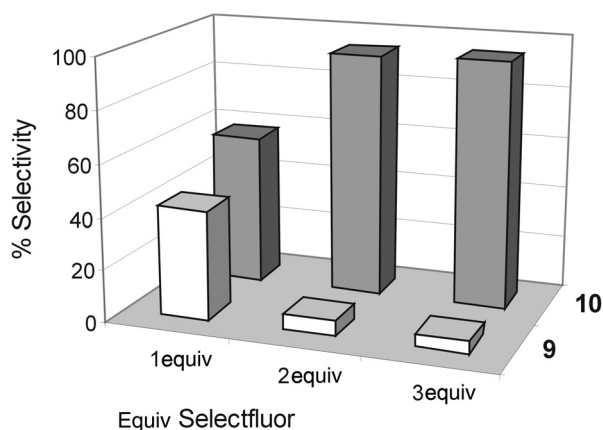


Figure 1 Electrophilic fluorination of **8** with Selectfluor. Standard Conditions: MeCN, 25 °C, 15 h. Percentages calculated from ^1H and ^{19}F NMR.

A more related reaction has recently been described, where 1-phenyl-substituted acetylenes could be transformed into their corresponding α,α -difluoro ketones, in presence of Selectfluor and Accufluor. However, the sub-

strate phenylacetylene resulted to be substantially less reactive than other phenyl-substituted alkynes.^{24,25}

In terms of mechanism, the reactions of substrate **8** with **7** to give α -fluorinated carbonyl compounds presumably proceed via direct transfer of the terminal alkenyl boryl moiety to the fluorine cation, whereas electrophilic fluorinations of alkenyltrimethylsilanes,²⁶ alkenyl organotin derivatives,²⁷ and alkenyl boronic acids²⁸ lead to the corresponding alkenyl fluorides. Further fluorination of the alkenyl α -fluoride boronate intermediate might provide the alkenyl α,α -difluoride boronate derivative, which is favored because of the excess of electrophilic fluorinating reagents in the reaction media. Finally, their treatment with a saturated aqueous sodium hydroxide solution could afford the oxidation of the internal alkenyl boryl unit to the carbonyl functional group. The regioselective electrophilic attack on the terminal alkenyl boryl unit might be related both to electronic (more nucleophilic) and steric factors (less hindered). Close regioselectivity was observed in the mono-cross coupling reaction of *cis*-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexen-1-ene with aryl halides, in the presence of $[\text{Pd}(\text{dppf})\text{Cl}_2]$ and K_2CO_3 as base, in DMF.¹³

Attempts to fluorinate the internal alkenyl boryl unit were unsuccessful even when *cis*-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)styrene (**8**) was treated with an aqueous solution of KHF_2 to obtain the corresponding alkenyl di-trifluoroborate, which is more reactive towards electrophilic fluorination.²⁸

Solvents other than acetonitrile have been used in the fluorination reaction, but none of them (toluene, THF, MeOH) has made it possible to carry out the electrophilic fluorination. Neither did the use of alternative electrophilic fluorination reagents such as 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**11**), 1-fluoropyridinium pyridine heptafluorodiborate (**12**), or *N*-fluorobenzenesulfonimide (**13**) (Figure 2) provide any expected fluorinated product.

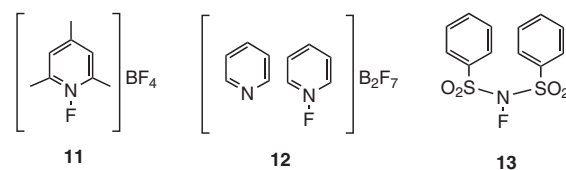
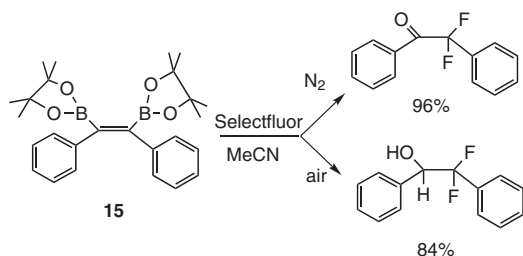


Figure 2

This previous work showed us the most favorable reaction conditions for obtaining the α,α -difluorinated carbonyl compound from substrate **8**. In this context we decided to conduct the same electrophilic reaction with Selectfluor on the alkenyl diboronates *cis*-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexene (**14**) and *cis*-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)stilbene (**15**). To our surprise, the aliphatic terminal alkyne did not provide any fluorinated compound whereas the internal alkyne was quantitatively converted into the correspond-

ing α,α -difluoroketone. When the electrophilic fluorination was carried out in presence of traces of H_2O or under air atmosphere, the product obtained was mainly the difluoromethyl alcohol (Scheme 4).



Scheme 4

We are now working on performing the tandem sequence diboration/fluorination in one global step. Towards this end, we need first to optimize the catalytic reaction conditions to perform the diboration under acetonitrile as the common solvent. These results and the scope of the one-pot reaction to other substituted internal and terminal alkynes will be published in due course.

Catalytic Diboration of Alkynes; Typical Procedure

Method A: To a sample of $[\text{Pt}(\text{NBE})_3]$ (0.025 mmol) dissolved in toluene (2 mL) under inert atmosphere was added PPh_3 (0.03 mmol). This solution was added to a mixture of the diboron reagent (1.1 mmol) dissolved in toluene (4 mL). The alkyne (1 mmol) was added to the solution and left until the reaction was complete. Purification was carried out by filtration over Celite and recrystallization with cold hexane.

Method B: To a sample of $[\text{Pt}(\text{PPh}_3)_4]$ (0.025 mmol) dissolved in DMF (2 mL) under inert atmosphere was added a mixture of the diboron reagent (1.1 mmol) dissolved in toluene (4 mL). The alkyne (1 mmol) was added to the solution and stirred at 80°C until reaction was complete. Then the reaction mixture was diluted with benzene, repeatedly washed with cold water to remove DMF, and finally dried over anhyd MgSO_4 . Kugelrohr distillation gave the alkenyl diboronate.

Electrophilic Fluorination of Alkenyl Diboronates; Typical Procedure

To a solution of alkenyl diboronate (1 mmol) in MeCN (6 mL), under inert atmosphere, Selectfluor (2 equiv) was added and the reaction mixture stirred at r.t. for 15 h. Then the solvent was removed under reduced pressure. The residue was treated with aq NaOH (5 mL, 1.0 M) and extracted with Et_2O (3×10 mL).

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