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Electrochemical Synthesis of *gem*-Difluoro- and γ-Fluoro-Allyl Boronates and Silanes

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Abstract: The electrochemical synthesis of fluorinated allyl silanes and boronates was disclosed. The addition of electrogenerated boryl or silyl radicals onto many α-trifluoromethyl or α-difluoromethylstyrenes in an undivided cell allowed the formation of a large panel of synthetically useful *gem*-difluoro and γ-fluoroallyl boronates and silanes (64 examples, from 31% to 95% yield). In addition, a scale up of the reactions under continuous flow was showcased using an electrochemical reactor with promising volumetric productivity (688 $g.L^{-1}.h^{-1}$ and 496 $g.L^{-1}.h^{-1}$). Moreover, the synthetic utility of these building blocks was highlighted through versatile transformations. Finally, plausible reaction mechanisms were suggested to explain the formation of the products.

Introduction

Molecules containing a fluorine atom or fluorinated groups are linchpins in the quest of pharmaceuticals and agrochemicals and are key building blocks in material science.[1] This particular role in organic synthetic chemistry results from the intrinsic properties of the fluorine atom.[2] Indeed, its electronegativity and small radius have a huge impact on the physicochemical properties of the molecules. The incorporation of a fluorine atom or fluorinated groups might alter the metabolic stability, the lipophilicity, or the conformation of the molecule.[3] At last but not least, the presence of fluorine can drastically change the H-bonding ability of a neighboring functional group, as well as its pKa, impacting the interactions of the molecules with biological receptors, for example. These features account for the ubiquity of fluorinated molecules in the portfolio of bioactive marketed molecules.[4] Hence, the design of strategies and reagents to efficiently forge fluorinated molecules is of high demand. Allyl silane and allyl boron derivatives are well recognized as strategic building blocks and reagents in the arsenal of organic practitioners to increase the molecular complexity.[5] Among the developed reactions, the highly important Hosomi-Sakurai and Brown allylation reactions are probably the most significant examples,[6] widely used in organic synthesis. Although, highly functionalized allyl silane and boronate derivatives were already synthesized, less attention was paid to the synthesis of the fluorinated derivatives, despite their conspicuous synthetic utility to forge fluorinated molecules. With respect to *gem*-difluoroallyl silanes, anionic pathways relying on a S_N2' reaction manifold with trifluoro- or bromodifluoromethylated olefins were initially reported [Scheme 1, Equation (1)&(2)].[7] Then, transition metal catalysis was beneficial to permit the addition of boron or silylated species onto trifluoromethylated olefins,[8] starting from either B_2Pin_2 or the Suginome reagent (i.e. $PhMe_2Si$–BPin), respectively [Scheme 1, Equation (3)]. Recently, as part of the impetus from the community on the development of photocatalytic processes, the addition of NHC-stabilized 7-electrons boryl radical was disclosed by Wu,[9a] Liu and Liu,[9b] independently [Scheme 1, Equation (4)]. Likewise, during the preparation of this manuscript, the addition of silyl radicals was reported using an Ir-photocatalyst or 4-CzIPN along with a HAT catalyst from silanes [Scheme 1, Equation (5)].[10] Noteworthy, the synthesis of γ-fluorinated allyl boronates remained restricted to a single example.[11]

Besides, organic electrochemistry is an attractive research field, which has witnessed and impressive renewal of interest over the last five years.[12] Indeed, taking into account the contemporary environmental concerns, the use of electrons as the reagent in chemical reaction is appealing. Electrons could replace hazardous and/or toxic reagents and when electricity arise from renewable sources (e.g. wind- or hydro-power), electrochemistry might contribute to the elaboration of more sustainable process. Hence, as part of our ongoing research program dedicated to organofluorine chemistry and organic electrochemistry,[13] we sought to develop a straightforward access to di-, and monofluorinated allyl silanes and allyl boronates. In that purpose, we conjectured that α-trifluoromethyl and α-difluoromethylstyrene derivatives would be the substrates of choice. These substrates, which have already been successfully used in radical addition reactions,[14]

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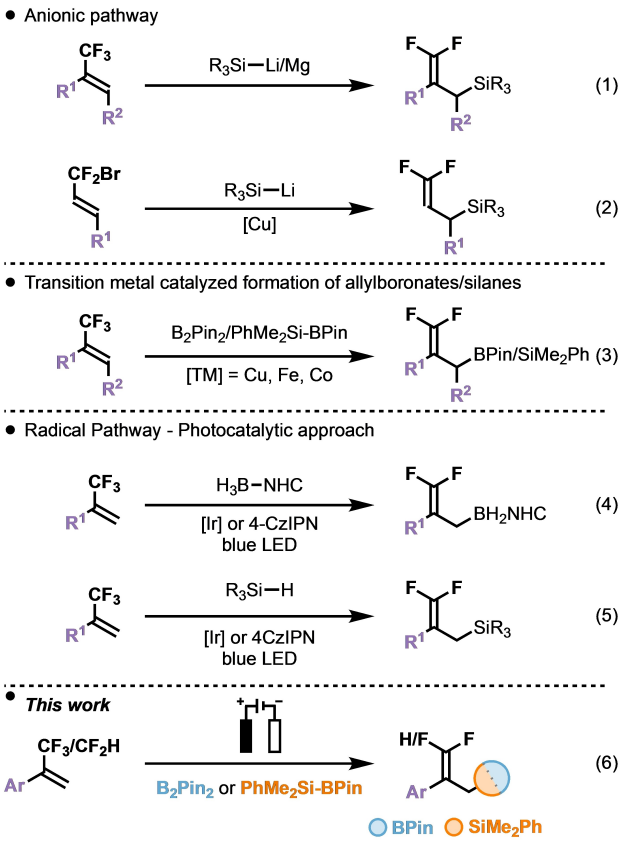
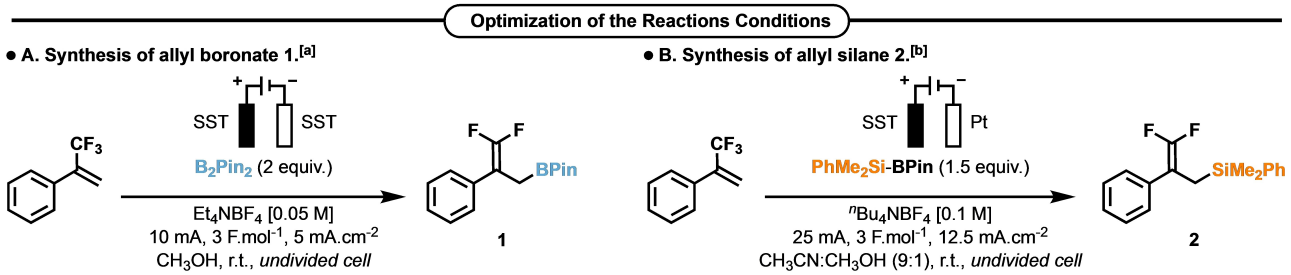


Scheme 1. State of the art and present work.

would react with the electrogenerated boryl or silyl radical. Subsequently to the addition, a reduction/fluoride elimination (E1cB) sequence would deliver the corresponding *gem*-difluoroallyl or γ-fluoroallyl boronates and silanes [Scheme 1, Equation (6)].

Results and Discussion

To assess our conjecture, the α-trifluoromethylstyrene was used as the model substrate and was tested in the borylation reaction. After a set of optimizations,[15] we have been able to obtained the *gem*-difluoroallyl boronate **1**. The reaction carried out in MeOH, using Et_4NBF_4 as the electrolyte (0.05 M), B_2Pin_2 as the boron reagent, stainless steel electrodes with a constant current of 10 mA and a charge of 3 F.mol^{-1}, allowed the formation of **1** in 79% ^{19}F NMR yield and 69% isolated yield (Scheme 2A, entry 1). From this optimization, we found that methanol as the solvent was crucial for the reaction outcome (entry 2). Moreover, the use of stainless steel electrodes at both the cathode and the anode was optimal, since other combinations led to a decrease of the reaction yield (entries 3 & 4). Other electrolytes were tested, but gave a lower yield into **1** (entry 5). Finally, a decrease of the current or the concentration of the reaction led to lower yields (entries 6 & 7). Likewise, α-trifluoromethylstyrene was used to optimize the synthesis of the *gem*-difluoroallyl silane **2**. After an optimization, we delineated the optimal reaction conditions for the formation of **2**.[15] The reaction with the Suginome reagent ($PhMe_2Si$–BPin) in a CH_3CN:CH_3OH mixture (9:1), using $^nBu_4NBF_4$ as the electrolyte (0.1 M), allowed the formation of **2** in a 95% ^{19}F NMR yield and 87% isolated yield. The reaction was performed under a constant current of 25 mA with a charge of 3 F.mol^{-1}, using a stainless steel anode and a platinum electrode as the cathode (Scheme 2B, entry 1). The CH_3CN:CH_3OH solvent mixture was



Entry	Variations from the standard conditions	Yield[c]
1	*none*	79%
2	CH_3CN:CH_3OH (9:1) instead of CH_3OH	36%
3	Pt cathode instead of SST cathode	64%
4	Pt anode instead of SST anode	0%
5	$^nBu_4NBF_4$ or $^nBu_4NOAc$ instead of Et_4NBF_4	< 67%
6	5 mA instead of 10 mA	55%
7	0.1 M instead of 0.05 M	42%

Entry	Variations from the standard conditions	Yield[c]
1	*none*	95%
2	CH_3OH instead of CH_3CN:CH_3OH (9:1)	27%
3	CH_3CN instead of CH_3CN:CH_3OH (9:1)	0%
4	Et_4NBF_4 instead of $^nBu_4NBF_4$	42%
5	$^nBu_4NOAc$ instead of $^nBu_4NBF_4$	34%
6	20 mA instead of 25 mA	86%
7	30 mA instead of 25 mA	70%

Scheme 2. Optimization of the reaction conditions. [a] Reactions conditions: α-trifluoromethyl styrene (0.2 mmol), B_2Pin_2 (0.4 mmol), Et_4NBF_4 [0.05 M] in MeOH (4 mL), r.t., stainless steel electrodes (anode&cathode), under air, electrolysis for 97 min. [b] Reactions conditions: α-trifluoromethyl styrene (0.4 mmol), Suginome reagent (0.6 mmol), $^nBu_4NBF_4$ [0.1 M] in CH_3CN:CH_3OH (9:1, 4 mL), r.t., stainless steel (anode), platinum (cathode), under air, electrolysis for 77 min. [c] Yield determined by ^{19}F NMR by using 2,2,2-trifluoroacetophenone as an internal standard.

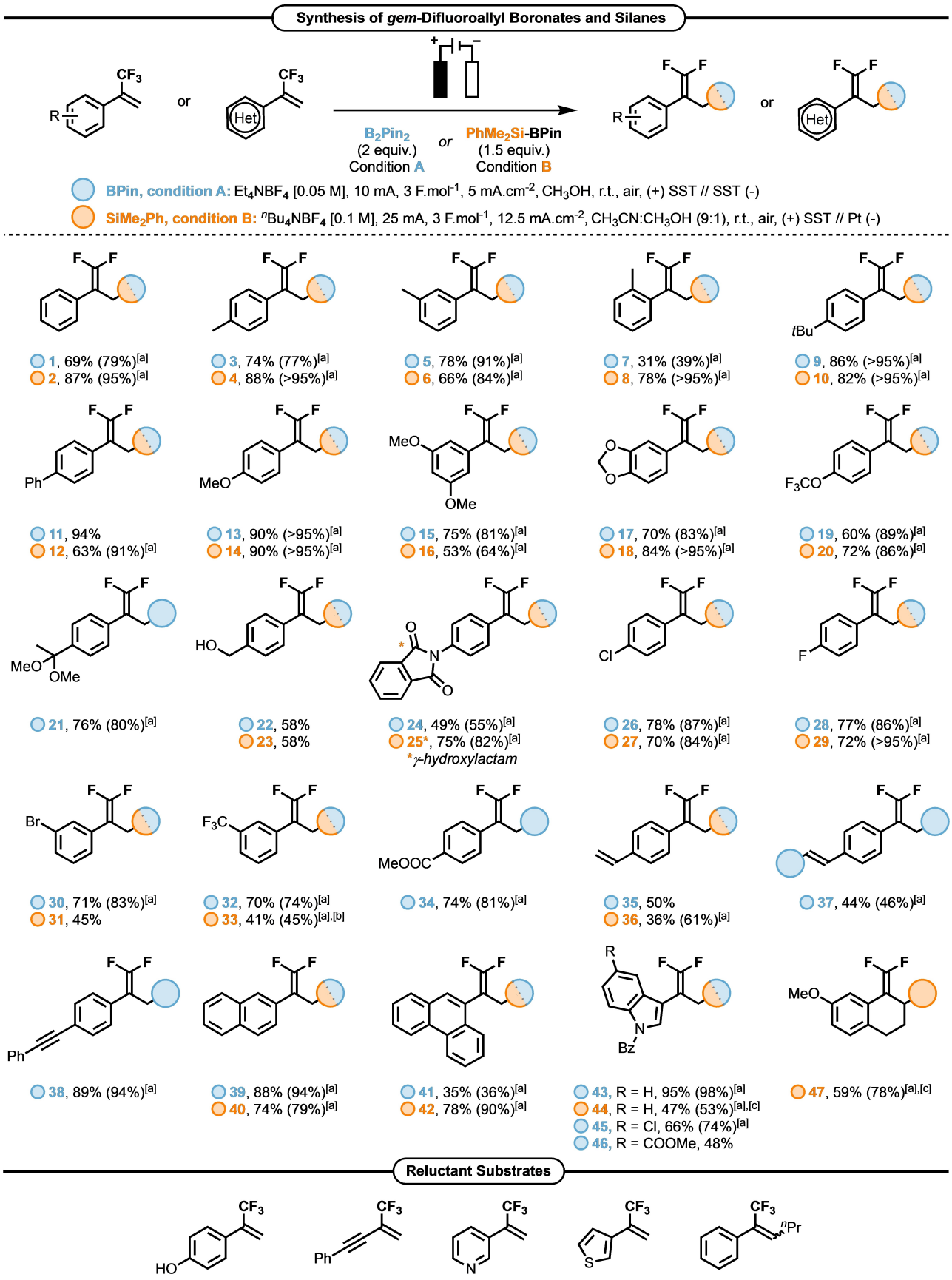
required to ensure the formation of **2** in a decent yield (entries 2 & 3), while other electrolytes furnished lower yields (entries 4 & 5). Finally, a current of 25 mA was the optimal one, since an increase or a decrease of this parameter led to lower yields into **2** (entries 6 & 7). Then, having settled the optimal reactions conditions for the formation of *gem*-difluoroallyl boronates and *gem*-difluoroallyl silanes, we moved on the evaluation of the scope of these transformations (Scheme 3). First, the substitution pattern on the aromatic ring of the styrene derivatives was studied. The introduction of a methyl group at the *para* or *meta* position did not affect the outcome of the borylation and silylation reactions, since the products **3**–**6** were isolated in good to excellent yields (from 66% to 88% yields). The addition of the boryl radical to the alkene was affected by the presence of an *ortho* substituent and **7** was isolated in 31% yield, in contrast to the addition of the silyl radical which provided **8** in an excellent 78% yield.

Then, both reactions were tested with substrates bearing electron-donating groups. The *gem*-difluoroallyl boronates and *gem*-difluoroallyl silanes **9**–**18** were isolated in good to excellent yields. Interestingly, the OCF_3 substituent, an important motif in drug discovery programs,[16] was tolerated and the boronate **19** and silane **20** were isolated in 60% and 72%, respectively. Acetal and benzylic alcohol residues were also compatible, as highlighted with the products **21**–**23**, which were isolated in moderate to good yields. Surprisingly, the presence of a phthalimide substituent did not affect the outcome of the borylation or silylation event, since **24** and **25** were formed in moderate to good yields (49% and 75%), however with the concomitant partial reduction of the phthalimide into the γ-hydroxylactam. Then, α-trifluoromethylstyrenes having a halogen substituent or a trifluoromethyl group on the aromatic ring were used in our reactions. Pleasingly, the borylated and silylated products **26**–**33** were isolated in decent yields (from 41% to 78% yield), albeit slightly lower for the formation of the allyl silanes. The presence of an ester residue was tolerated for the addition of the boryl radical (**34**), while no formation of the silanes was witnessed using the optimized reaction conditions. Then, the reaction was tested with the α-trifluoromethylstyrene bearing an olefin at the *para* position. Both borylation and silylation reactions were selective toward the addition on the fluorinated alkenes, since no addition on the vinyl residue was observed. The corresponding products **35** and **36** were obtained in good yields, albeit with lower isolated yields for the silanes due to a tedious purification. However, the presence of a terminal alkyne at the *para* position led to the concomitant addition of the boryl radical to the alkyne and trifluoromethylalkene, giving the bis-borylated product **37** in 44% isolated yield. In contrast, the presence of a substituted alkyne at the *para* position led to the sole borylation of the trifluoromethylated alkene (**38**), the internal alkyne being untouched. Note that the formation of the corresponding allyl silanes was inefficient on these substrates bearing an alkyne. Other aromatic substituents were used to evaluate the scope of these transformations. 2-Naphthyl and 9-phenanthryl derivatives **39**–**42** were readily obtained in moderate to good yields. Then, the reaction was tested on indole derivatives and pleasingly both allyl boronates and silanes **43**–**46** were isolated in moderate to very good yields (from 47% to 95% yields). Finally, the silylation of a cyclic trisubstituted trifluoromethylated alkene was performed, and **47** was isolated in 59% yield. Surprisingly, no reaction was observed with regard to the addition of the boryl radical. Unfortunately, some substrates were reluctant in both formation of *gem*-difluoroallyl boronates and silanes. The presence of a phenol was deleterious, probably due to side oxidation reaction. Likewise, enyne led to no conversion, while other heteroaromatic (pyridine or thiophene) led to messy reaction mixtures without trace of the desired products. Finally, non-cyclic trisubstituted olefin remained unreactive under our reaction conditions and starting material was recovered.

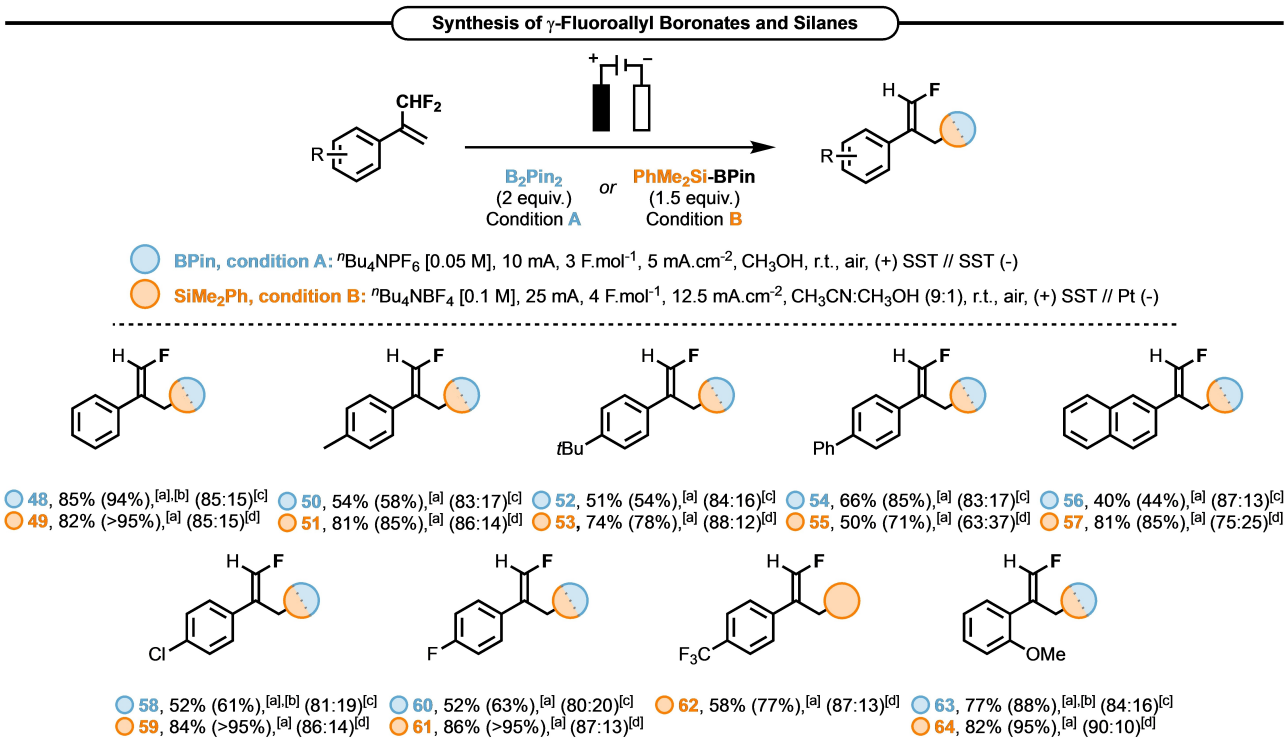
Next, we sought that our reactions conditions could be extended to the formation of γ-fluoroallyl boronates and silanes from α-difluoromethylstyrene derivatives (Scheme 4). Pleasingly, under slightly modified reaction conditions the α-difluoromethylstyrene was readily converted into the boronate **48** and silane **49** in excellent yield (85% and 82%, respectively) and a decent 85:15 diastereoisomeric ratio. Then, the reaction was extended to the formation of γ-fluoroallyl boronates and silanes bearing electron-donating group on the aryl ring and the products **50**–**55** were isolated in moderate to good yields (from 50% to 81% yields) and moderate to good diastereoisomeric ratio (from 63:37 to 88:12). The reaction was also extended to the 2-naphthyl derivatives **56** and **57**. Chloride, fluoride and trifluoromethyl substituents were also introduced and the reaction efficiency was not altered (**58**-**62**). Finally, the *ortho* substituted derivatives **63** and **64** were obtained in very good yields and diastereoisomeric ratio.

Then, aware of the tedious scale up of electrochemical transformations,[17] we aimed at showcasing the possible extension of these transformations under continuous flow conditions to address this longstanding problem under batch conditions (Scheme 5A). After an extensive set of optimizations,[15] the borylation of the α-trifluoromethyl-*para*-methoxystyrene was developed in a 0.6 mL electrochemical reactor. Using a current density of 16.7 $mA.cm^{-2}$ and a 10-fold decrease of the electrolyte concentration, the *gem*-difluoroallyl boronate **13** was isolated in 74% yield with a volumetric productivity of 688 $g.L^{-1}.h^{-1}$. Likewise, we have been able to extend the formation of the *gem*-difluoroallyl silane **14** under continuous flow conditions. Using a current density of 12.5 $mA.cm^{-2}$ and a concentration of electrolyte divided by 10 in a 0.6 mL electrochemical reactor, the product **14** was obtained in 78% yield with a volumetric productivity of 496 $g.L^{-1}.h^{-1}$. These results represent a promising proof of concept for further optimizations of the scale up of these two reactions, particularly on longer reaction time,[18] to tackle the limitations of synthetic electrochemistry in batch.

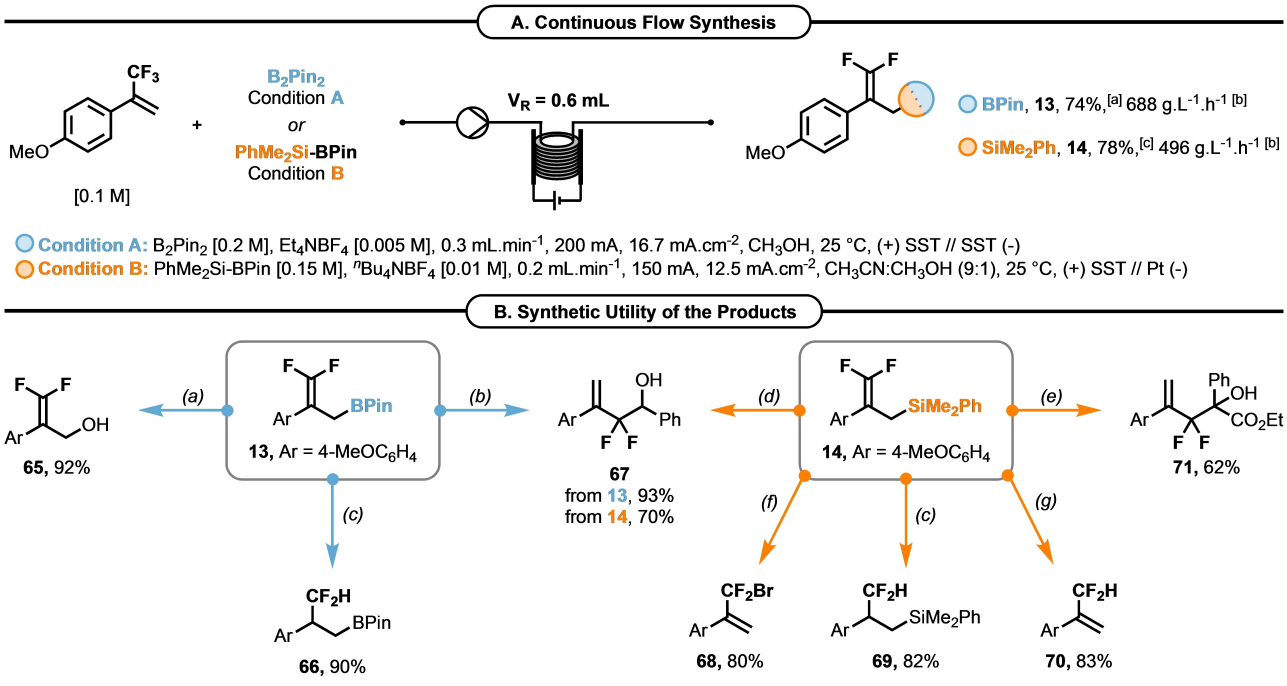
Then, we highlighted the synthetic utility of the *gem*-difluoroallyl boronates and silanes (Scheme 5B). The *gem*-difluoroallyl boronate **13** was readily oxidized into the corresponding allylic alcohol **65** in 92% isolated yield. Access to the alkyl boronate **66** was showcased after the hydrogenation of the olefin residue using Pd/C as the catalyst. Then, boronate **13** was used in a classical allylation reaction with benzaldehyde to



Scheme 3. Evaluation of the scope of the electrochemical synthesis of *gem*-difluoroallyl boronates and *gem*-difluoroallyl silanes. Reactions were carried out on 0.4 mmol scale. Isolated yields were given. [a] Yields determined by ^{19}F NMR by using 2,2,2-trifluoroacetophenone as an internal standard. [b] 1.6 F.mol^{-1} instead of 3 F.mol^{-1}. [c] 4.5 F.mol^{-1} instead of 3 F.mol^{-1}.



Scheme 4. Electrochemical synthesis of γ-fluoroallyl boronates and silanes - scope of the reaction. Reactions were carried out on 0.4 mmol scale. Isolated yields were given. [a] Yields determined by ^{19}F NMR by using 2,2,2-trifluoroacetophenone as an internal standard. [b] Et_4NBF_4 instead of $^nBu_4NPF_6$. [c] *E:Z* ratio determined by ^{19}F NMR on the crude of the reaction mixture. [d] *Z:E* ratio determined by ^{19}F NMR on the crude of the reaction mixture.

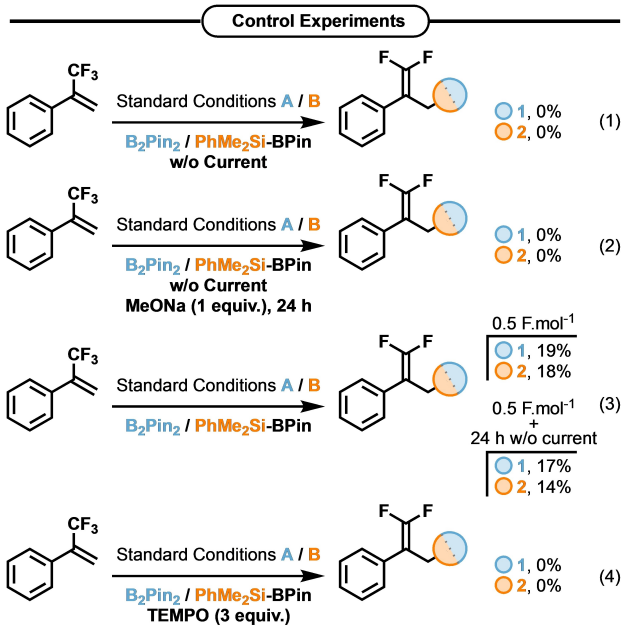


Scheme 5. A. Continuous flow synthesis of *gem*-difluoroallylboronates and silanes **13** and **14**. B. Synthetic utility of the products. [a] Isolated yield on a 2.5 mmol scale. [b] Volumetric productivity. [c] Yields determined by ^{19}F NMR by using α,α,α-trifluorotoluene as an internal standard on a 0.5 mmol scale. *(a)* **13** (0.3 mmol), $NaBO_3$•$4H_2O$ (0.9 mmol), THF:H_2O (1:1, 6 mL), r.t., 3 h. *(b)* **13** (0.3 mmol), PhCHO (0.45 mmol), $(PHO)_2PO_2H$ (10 mol%), $PhCO_2H$ (10 mol%), toluene (2 mL), 65 °C, 15 h. *(c)* **13** (0.3 mmol), Pd/C (10 wt%, 3 mol%), H_2 (1 atm.), MeOH (3 mL), r.t., 12 h. *(d)* **14** (0.25 mmol), PhCHO (0.5 mmol), Me_4NF (0.3 mmol), DMF (1 mL), −10 °C, overnight. *(e)* **14** (0.25 mmol), $Ph(CO)CO_2Et$ (0.21 mmol), $SnCl_4$ (0.21 mmol), CH_2Cl_2 (1 mL), r.t., 20 min. *(f)* **14** (0.25 mmol), NBS (0.38 mmol), CH_3CN (1.1 mL), 50 °C, overnight. *(g)* **14** (0.25 mmol), H_2O (0.75 mmol), TBAF (0.75 mmol), THF (1 mL), 0 °C to 65 °C, 2 h.

provide the difluoromethylated homoallylic alcohol **67** in 93% yield. In the same vein, the reaction of the allyl silane **14** with benzaldehyde gave **67** in a 70% isolated yield. The synthetic utility of **14** was further demonstrated in the bromination reaction, giving **68** in 80% isolated yield. The reduction was also carried out to afford the aliphatic derivative **69** in 82% yield, while the α-difluoromethyl-*para*-methoxystyrene **70** was obtained in 83% yield after reaction with TBAF in the presence of water. Finally, **14** was used in a Hosomi-Sakurai reaction with ethyl benzoylformate, giving the tertiary alcohol **71** in 62% yield.

Then, to gain insights into the mechanism of these reactions some control experiments were performed (Scheme 6). First, the reactions were performed without current and no product formation was observed, demonstrating the requirement of electricity for this transformation [Scheme 6, Equation (1)]. The addition of NaOMe (1 equiv.) to reaction mixture was evaluated [Scheme 6, Equation (2)]. In the absence of current, the reactions did not proceed, showing that the reactions were not promoted by the sole in situ generation of methoxide anion, resulting from the reduction of methanol. Then, to preclude the involvement of released salts from the electrodes as possible catalysts for this transformation, the electrochemical reactions were stopped after 16 and 13 minutes (0.5 F.mol^{-1}), respectively, and stirred for an additional 24 h [Scheme 6, Equation (3)]. As expected, no increase of the reaction yields was measured, precluding the involvement of metallic salts as catalysts/promoters in these transformations.

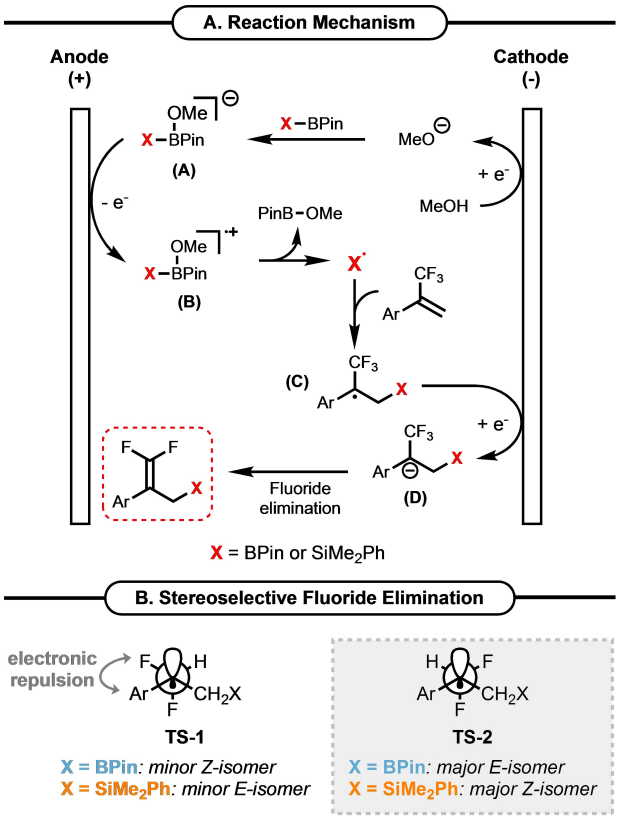
Complementary to these experiments, both reactions were conducted in the presence of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) and no formation of the products **1** and **2** was observed [Scheme 6, Equation (4)]. These results suggested the involvement of radical species in the reaction mechanism.



Scheme 6. Control experiments.

With these results in hand and the reports from the literature,[14b,f,h] we suggested the following mechanism for these transformations (Scheme 7A). First, B_2Pin_2 or the Suginome reagent reacts with the in situ formed methoxide to form the corresponding borate **A**. Then, an oxidation event at the anode generates the radical cation **B**, which quickly collapse into either the boryl or silyl radical.[19] Note that in the case of the boryl radical, the latter is probably stabilized as a 7-electrons boryl radical by coordination with the solvent (i.e. CH_3CN or CH_3OH) or a methoxide anion.[20] Then, a radical addition onto the α-trifluoromethylstyrene affords the benzylic radical **C**. A reduction of latter provides the anion **D**, which subsequently undergoes an E1cB elimination reaction to deliver the *gem*-difluoromethylallyl boronates or silanes. Regarding the reaction with α-difluoromethylstyrene derivatives, a similar reaction is suggested.

To explain the observed diastereoselectivity, a Newman projection of the two possible conformers, leading either to the *E* or *Z* isomers after antiperiplanar fluoride elimination is suggested (Scheme 7B). The predictive model **TS-1**, suggesting the formation of the *Z*-isomer,[21] exhibits a documented unfavorable electronic repulsion between the fluorine atom and the aromatic residue.[22] Conversely, the model **TS-2**, which predict access to the *E*-isomer, does not showcase such repulsion.



Scheme 7. A. Plausible reactions mechanisms. B. Stereochemical outcome of the reaction with α-difluoromethylstyrenes.

Conclusion

In summary, we disclosed herein the practical electrochemical synthesis of *gem*-difluoroallyl boronates and silanes. In an open-air undivided cell, the desired products were obtained in good to excellent yields (47 examples, from 31% to 95% yields). Under identical reactions conditions, the synthesis of γ-fluoroallyl boronates and silanes was achieved in good yields, and good diastereoselectivities (17 examples, from 40% to 86% yields, up to 90:10 diastereoisomeric ratio). In addition, a possible scale up of these reactions was demonstrated under continuous flow conditions with promising volumetric productivities. These reactions showcased an excellent functional group tolerance, offering a large panel of interesting fluorinated building blocks and their versatility was highlighted in synthetically useful transformations. Finally, plausible mechanisms were suggested to explain the formation of these strategic molecules. We hope that this practical method will be useful and will contribute to the synthesis of complex fluorinated molecules.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: allyl boronates · allyl silanes · electrochemistry · fluorine · trifluoromethylated alkenes

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