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Building Functionality through Sequential C–B and C–F Bond Formation

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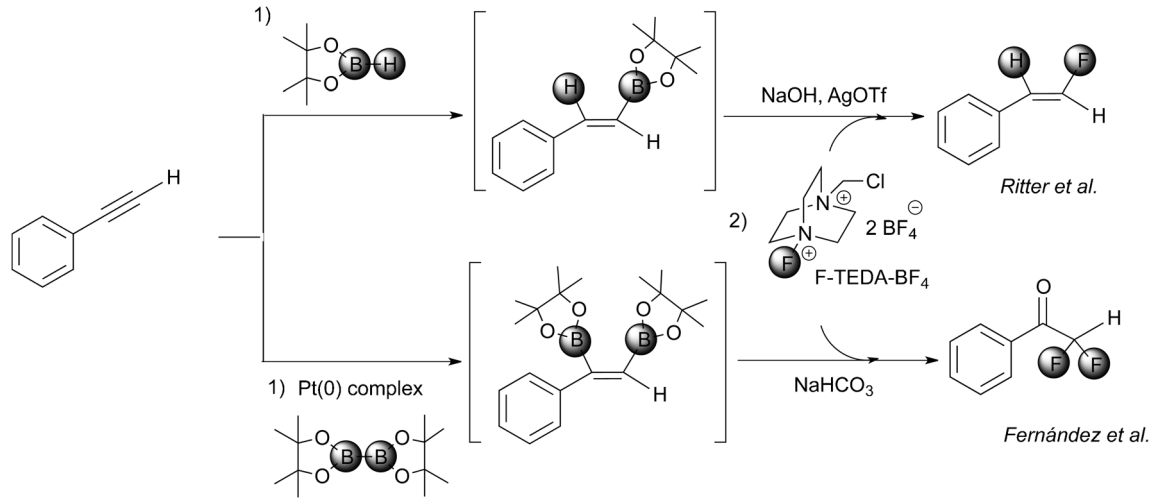
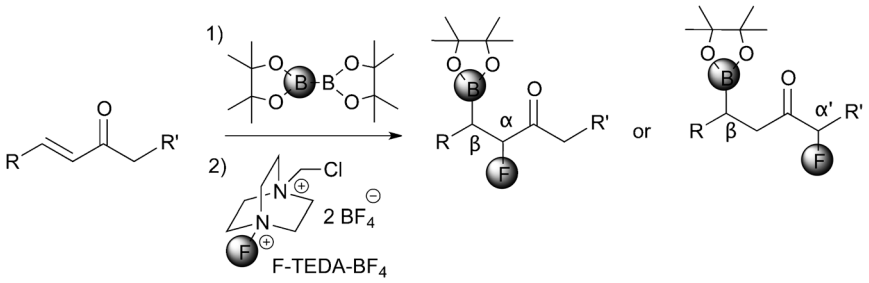
Abstract: α′-Fluoro β-boryl ketones can be efficiently synthesised from a sequential organocatalytic β-boration pathway and consecutive electrophilic fluorination reaction in an acidic medium. Alternatively, the regioisomers of α-fluoro β-boryl ketones can be diastereoselectively obtained from Cu(I)-mediated β-boration followed by *in situ* fluorination of the boron enolate. Enantioenriched mixtures of the major *anti*-diastereomer of vicinal C–B and C–F bonds are found in the presence of the chiral ligand QuinoxP*.

Keywords: β-boration; copper catalysts; α-fluorination; organocatalysis; regioselectivity

Current emphasis on the development of multiple chemical transformations sequentially performed in a single reaction vessel, without intermediary purification steps, has led to the generation of molecular complexity in a concise fashion.[1,2] The benefits are based on reduced time, costs, and waste generation, but compatibility and reliability must be circumvented to become attractive for industrial purposes.[1] In this context, the combination of the fluorination reaction with reported C–B bond forming reactions has increased the utility of organoboranes in the synthesis of organofluorides. *One-pot* strategies combining hydroboration or diboration of alkynes followed by fluorination of the alkenyl-monoborated or diborated intermediates, afforded efficient routes to polyfunctional compounds without intermediate purification steps (Scheme 1).[3,4] These strategies precisely transform the C-boryl moiety into a C–F bond. Here we address a new synthetic target by developing a *one-pot* transformation of α,β-unsaturated ketones into α-fluoro β-boryl ketones or α′-fluoro β-boryl ketones, *via* a very selective C–B and C–F sequential bond formation (Scheme 2).



Scheme 1. *One-pot* strategies of fluorination of alkenylboronate intermediates.



Scheme 2. Regioselective *one-pot* nucleophilic β-boration/electrophilic fluorination studied in this work.

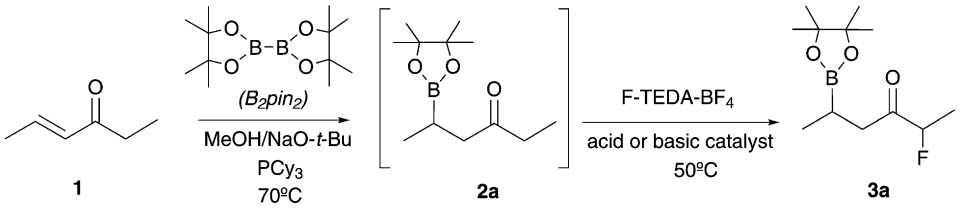
Our aim is to preserve both functionalities during the sequential reaction to provide a new palette of polyfunctional molecules, in a highly regioselective way. To achieve this goal we suggest the strategy based on nucleophilic β-boration of activated olefins followed by electrophilic fluorination. To guarantee the most condition-tolerant method for the sequential functionalisation, we explored two approaches towards β-boration: the metal-mediated β-boration of activated olefins,[5–13] and the organocatalytic β-boration.[14–18] It was proved that the reagents were compatible during the sequential reactions and that the methodology could be used in a series of substrates. To the best of our knowledge, this is the first attempt to prepare and isolate organofluroboryl ketones, despite their inherent interest for biomedical applications.[19]

We started by considering the simplest described method to activate the diboron source B_2pin_2 with MeOH/base, and forming the Lewis base $MeO^- \rightarrow$ bis(pinacolato)diboron adduct (**A**).[16,20] The mixture of **A** with 4-hexen-3-one (**1**), as the model substrate selected, favoured the nucleophilic attack[21] of the sp^2 boryl moiety at the β-position of the activated ketone. Within 2 h, at 70 °C, total conversion of the substrate into the corresponding β-borated product, 5-(pinacol)-borylhexen-3-one (**2a**) was achieved (Table 1). Further reactivity was explored without isolation of **2a**, by addition of F-TEDA-BF_4 as the electrophilic fluorinated reagent in the presence of pyrrolidine.[22,23] However, the reaction did not proceed to the formation of any major product and only 4% of the substrate was converted into α′-fluorinated β-borated ketone (Table 1, entry 1). The characterisation of product **3a** reveals that the new C–F bond was exclusively formed in the $C_{\alpha'}$ of the ketone.

We then turned our attention to an alternative electrophilic fluorination protocol *via in situ* formation of a nucleophilic enol intermediate under acidic conditions. The efficiency of this direct electrophilic fluorination of ketones has recently been demonstrated by Batey and co-workers.[24] Since this reaction has been reported to proceed most efficiently in MeOH, we found a principle of compatibility with the organocatalytic β-boration carried out in MeOH as solvent. Therefore, the organocatalytic β-boration followed by the addition of 1 equiv. of F-TEDA-BF_4 and H_2SO_4 (10 mol%) transformed **1** into the corresponding α′-fluoro β-(pinacol)boryl ketone (**3a**) with a conversion of 29% (Table 1, entry 2). The need for an excess of fluorinating reagent was justified by the higher conversion observed on **3a**, when 2 equiv. of F-TEDA-BF_4 were used (60% isolated yield, Table 1, entry 3).

To highlight the efficiency of the *one-pot* sequence, we performed a parallel study in which 2 equiv. of F-TEDA-BF_4 were added to an isolated β-borated ketone **2a**. Under identical conditions, the electrophilic fluorination transformed **2a** into **3a** with slightly higher conversion (74% isolated yield, Table 1, entry 4). The amount of sulphuric acid was also optimised to 10 mol% because greater amounts of the acid catalyst did not significantly improve the yield (Table 1, entries 5 and 6) and lower amounts decreased the reaction outcome (Table 1, entry 7). The application of other acid catalysts, such as HNO_3 (Table 1, entry 8), HCOOH and CF_3COOH was less efficient in this direct electrophilic fluorination. Alternative fluorinating reagents,[22] such as *N*-fluorobenzenesulfonimide (NFSI) and 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (1-F-2,4,6-Me_3PyBF_4), were inefficient under optimised reaction conditions. The sequential C_β–B and C_α–F bond formation was also extended to the use of other diboron reagents. When bis(neopenthylglycolato)diboron (B_2neop_2) or bis-(hexyleneglycolato)diboron (B_2hex_2) were used instead of B_2pin_2, substrate **1** was quantitatively β-borated and consecutive electrophilic fluorination, led to the formation of the corresponding α′-fluoro β-boryl ketones **3b** and **3c**, respectively (Table 2, entries 1 and 2). It should be pointed out that the *one-pot* synthesis of α′-fluoro β-boryl ketones **3a**, **3b** and **3c** was carried out with total regioselectivity but as a 1:1 mixture of diastereoisomers. The substrate scope included other α,β-unsaturated ketones, such as 1-penten-3-one (**4**) and 5-methyl 2-hepten-4-one (**6**). Under optimised reaction conditions, terminal substrate **4** was totally β-borated with B_2pin_2 within 2 h, and subsequent fluorination led to the α′-fluoro β-(pinacol)boryl ketone **5** with a conversion of up to 68% (Table 2, entry 3). The more hindered substrate **6** was also efficiently β-

Table 1. *One-pot* organocatalytic nucleophilic β-boration/electrophilic fluorination of 4-hexen-3-one.[a]

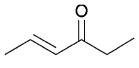
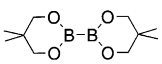
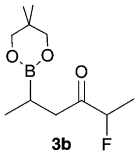
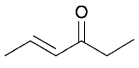
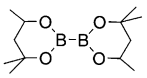
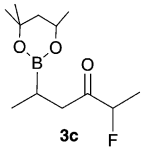
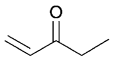
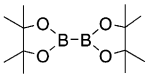
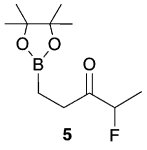
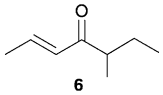
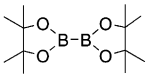
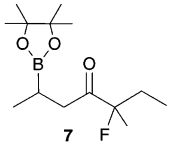


Entry	Substrate	Acid or basic catalyst	Conversion [%][b]	Isolated Yield of **3a** [%]
1	**1**	pyrrolidine (1 equiv.)	4	
2[c]	**1**	H_2SO_4 (10 mol%)	29	
3	**1**	H_2SO_4 (10 mol%)	63	60
4	**2a**	H_2SO_4 (10 mol%)	84	74
5	**1**	H_2SO_4 (20 mol%)	71	67
6	**2a**	H_2SO_4 (20 mol%)	86	75
7	**1**	H_2SO_4 (5 mol%)	33	
8	**1**	HNO_3 (10 mol%)	16	

[a] *Standard conditions for organocatalytic β-boration:* substrate (0.25 mmol), B_2pin_2 (1.1 equiv.), PCy_3 (10 mol%), NaO-*t*-Bu (5 mol%), MeOH (2 mL), 70 °C, 2 h. *Standard conditions for electrophilic fluorination of reaction mixture containing **2a**:* with pyrrolidine: F-TEDA-BF_4 (0.5 mmol), pyrrolidine (0.25 mmol), DMF (1 mL), 15 h; with acid: Selectfluor (0.25 or 0.5 mmol), H_2SO_4 95% (10 mol%, 0.025 mmol), 50 °C, 15 h.
[b] Conversion calculated by GC and NMR spectroscopy.
[c] F-TEDA-BF_4 (0.25 mmol).

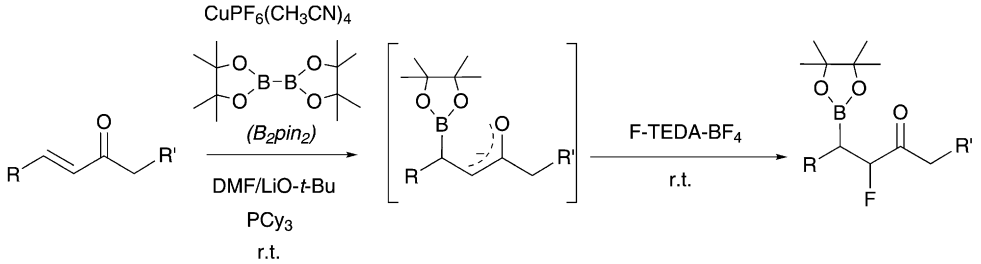
borated (>99%) and the electrophilic fluorination also took place regioselectively at the substituted $C_{\alpha'}$ but with lower conversion (Table 2, entry 4). The regioselective α′-electrophilic fluorination of the β-borated ketones seems to be controlled by the more thermodynamically stable enol intermediate.[24]

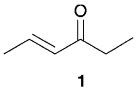
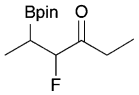
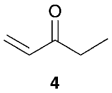
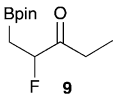
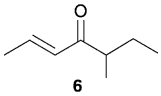
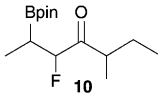
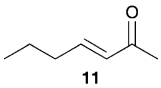
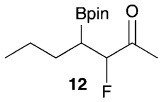
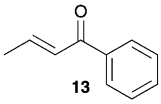
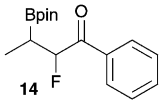
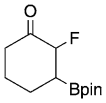
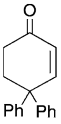
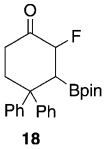
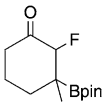
Table 2. Scope of α′-fluoro β-boryl ketones from α,β-unsaturated ketones.[a]

Entry	Substrate	Diboron Reagent	Product	Conversion [%][b]	Isolated Yield [%]
1				70	61
2				73	
3				68	
4				56	51

[a] *Standard conditions for organocatalytic β-boration towards >99% of β-borated ketone:* substrate (0.25 mmol), B_2pin_2 (1.1 equiv.), PCy_3 (10 mol%), NaO-*t*-Bu (5 mol%), MeOH (2 mL), 70 °C, 2 h. *Standard conditions for electrophilic fluorination:* F-TEDA-BF_4 (0.5 mmol), H_2SO_4 95% (10 mol%, 0.025 mmol), 50 °C, 15 h.
[b] Conversion calculated by GC and NMR spectroscopy

Table 3. Scope of α-fluoro β-boryl ketones from α,β-unsaturated keones.[a]



Entry	Substrate	Product	Conversion [%][b]	Isolated Yield [%]	*syn/anti* (*dr*)
1	 **1**	 **8a**	94	30	23/77
2	 **4**	 **9**	87		–/–
3	 **6**	 **10**	75	60	22/78
4	 **11**	 **12**	72		22/78
5	 **13**	 **14**	99	17[c]	20/80
6	 **15**	 **16**	99	20[c]	33/67
7	 **17**	 **18**	99	90	40/60
8	 **19**	 **20**	99	87	10/90

[a] *Standard conditions*: $Cu(CH_3CN)_4PF_6$ (0.025 mmol), PCy_3 (0.025 mmol) substrate (0.25 mmol), B_2pin_2 (1.1 equiv., 0.35 mmol), LiO-*t*-Bu (0.015 mmol) DMF (2 mL), room temperature, 2 h, after that period F-TEDA-BF_4 (0.5 mmol), room temperature, 16 h.

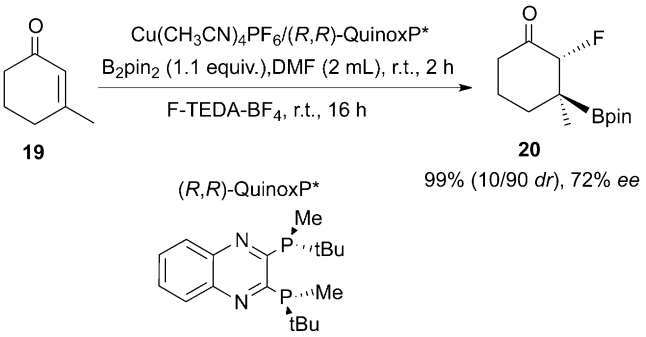
[b] Conversion calculated by GC and NMR spectroscopy.

[c] Isolated as the single minor diastereoisomer.

At this point we became interested in finding an alternative route for synthesising α-fluoro β-(pinacol)-boryl ketone from a wide range of aliphatic cyclic and open chain α,β-unsaturated ketones. To this end, we turned our attention to the Cu(I)-mediated β-boration of activated olefins[5–7] and we replaced MeOH by non-protic solvents. Inspired by the work of Shibasaki and co-workers,[7g] who found an efficient copper-based catalytic system to perform the β-boration of α,β-unsaturated ketones in DMF, we selected $Cu(CH_3CN)_4PF_6$ as the copper source and LiO-*t*-Bu as the base. When we carried out the copper catalysed β-boration reaction of **1** (150 min), followed by the addition of 2 equiv. of F-TEDA-BF_4 (16 h), we observed the quantitative formation of a new regioisomer **8a**, in which C–F was formed vicinal to the C–B bond. Substrate **1** was completely transformed and only a small percentage of non-fluorinated β-borated ketone was detected (Table 3, entry 1). In this particular case, the *anti* diastereoisomer was prefentially

formed *versus* the *syn* diastereoisomer (23/77 *dr*). The major *anti* isomer was characterised by comparison with the reported analogue α-fluoro-β-amino esters synthesised following a similar strategy of conjugate addition of lithium amides to α,β-unsaturated esters and sequential electrophilic fluorination.[25] In our case, the substrate scope was then investigated under optimised reaction conditions (Table 3) to establish the extension of this methodology. In general the C_β–B bond can be quantitatively formed from the conjugate B addition in all the substrates studied and the efficiency of the fluorination step on the copper enolate, as well as the diastereoselective ratio (*dr*), seem to be dependent on the nature of the substrate. Terminal substrate **4** could be totally β-borated with B_2pin_2 within 2 h, and subsequent fluorination led to the α-fluoro β-(pinacol)boryl ketone **9** with a conversion of up to 87%, as a single isomer (Table 2, entry 2).

When the long-chain aliphatic ketones 5-methyl-2-hepten-4-one (**6**) and 3-hepten-2-one (**11**) were subjected to the sequential β-boration/α-fluorination, the substrates were converted into the desired products **10** and **12** up to 75–87%, with identical diastereoselectivity (22/78 *dr*) in favour of the *anti* isomer (Table 3, entries 3 and 4). The more hindered substrate 1-phenyl-2-buten-1-one (**13**) was quantitatively converted into the corresponding α-fluoro β-(pinacol)boryl ketone **14**, with a slight increase in the diastereoselectivity (20/80 *dr*). But the more subtle differences in diastereoselectivity were observed in the sequential C–B and C–F bond formation of cylcohexenone **15** and substituted derivatives **17** and **19**. Despite the fact that in all cases the α-fluoro β-boryl ketones were quantitatively formed, the lower diastereoselectivity observed was in the β-boration α-fluorination of 4,4-diphenyl-2-cyclohexen-1-one (**17**) (40/60 *dr*) (Table 3, entry 7). However, the 3-methyl-2-cyclohexen-1-one (**19**) provided the higher diastereoselectivity on the *anti* isomer (10/90 *dr*) (Table 3, entry 8). It is interesting to note that, to the best of our knowledge, there is only one precedent in the literature in which the corresponding boron enolate from 3-substituted 2-cyclohexen-1-one, reacted further with benzaldeyde as an electrophile reagent to generate the corresponding aldol product with (6.5/1 *dr*).[7g] In that precedent, the enantioselective conjugate boration [using $Cu(CH_3CN)_4PF_6$ modified with the chiral ligand QuinoxP*] provided the tetrasubstituted carbon with a high level of enantioselectivity which was preserved during the sequential aldol/oxidation reaction.[7g] With this elegant precedent in mind, we decided to perform the copper-catalysed conjugate boration in an asymmetric way to further react the boron enolate with F-TEDA-BF_4. The substrate 3-methyl-2-cyclohexen-1-one (**19**) was β-borated with $Cu(CH_3CN)_4PF_6$/QuinoxP*[7g] to generate the quaternary C_β–B bond with



Scheme 3. Enantioselective *one-pot* nucleophilic β-boration/electrophilic fluorination sequence.

72% *ee* (Scheme 3). Subsequent α-fluorination of the enantioenriched boron enolate produced the α-fluoro β-(pinacol)boryl ketone **20** with 72% *ee* as a consequence of the retention of the asymmetric induction (Scheme 3). The advantage of this synthetic methodology is due to the simplicity in the enantioselective construction of the C_{sp3}–F bond.[26] This synthetic approach represents an alternative to the current efforts to develop enantioselective aliphatic electrophilic fluorinations routes.[3d,27,28]

In conclusion, we have developed two regioselective sequential protocols towards α′-fluoro β-boryl ketones and α-fluoro β-boryl ketones without precedent in the literature. The α′-fluoro β-boryl ketones were obtained by using a sequential organocatalytic β-boration of α,β-unsaturated ketones and a consecutive electrophilic fluorination reaction in an acidic medium. Compatibility with different diboron reagents has also been demonstrated. Alternatively, α-fluoro β-boryl ketones were synthesised in high yields as an enriched mixture of the *anti* diastereomer, by copper-mediated β-boration followed by *in situ* electrophilic fluorination of the boron enolate. When the conjugate B addition was performed enantioselectively, the transient enantioenriched mixture of the boron enolate reacted with the electrophilic fluorinating reagent providing a new asymmetric C_{sp3}–F bond.

Experimental Section

Organocatalytic β-Boration of α,β-Unsaturated Carbonyl Compounds Followed by Acid-Catalyzed α-Fluorination

Diboron reagent (1.1 equiv., 0.27 mmol), [normally bis(pinacolato)diboron], NaO-*t*-Bu (5 mol%, 0.01 mmol) and PCy_3 (10 mol%, 0.025 mmol) were transferred into an oven-dried Schlenck tube under an argon atmosphere. MeOH (2 mL) was then added. The mixture was stirred for 10 min at room temperature before the α,β-unsaturated ketone used as substrate (0.25 mmol) was added to the reaction mixture. The reaction mixture was stirred at 70 °C for 2 h (unless longer

time is required to complete the β-boration step). After that period, an aliquot was analysed by GC to determine the complete β-boration–α-protonation of the substrate. Afterwards, catalytic amounts of H_2SO_4 95% (10 mol%, 0.02 mmol) and fluorinating reagent (2 equiv., 0.50 mmol) (normally F-TEDA-BF_4) were added and the reaction was contuinued overnight with heating at 50 °C. The reaction mixture was cooled down, the precipitate formed was filtered and the solvent removed by rotary evaporation. Afterwards, EtOAc (4 mL) and water (2 mL) were added to the dry crude reaction mixture. The organic layer was collected, dried over $MgSO_4$ and concentrated gently on a rotary evaporator at 40 °C. An aliquot was diluted in deuterated chloroform and analysed by GC and ^{1}H NMR to determine conversion.

General Experimental Procedure for the Copper Catalytic β-Boration–α-Fluorination of α,β-Unsaturated Ketones

$Cu(CH_3CN)_4PF_6$ (0.025 mmol), bis(pinacolato)diboron (0.35 mmol), LiO-*t*-Bu (0.015 mmol), PCy_3 (0.025 mmol) were transferred into an oven-dried Schlenck tube under an argon atmosphere. DMF (2 mL) was then added. The mixture was stirred for 10 min at room temperature before the α,β-unsaturated ketone used as substrate (0.25 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2.5 h. Afterwards, the fluorinating reagent F-TEDA-BF_4 (0.5 mmol) was added to the reaction mixture and the reaction was continued at room temperature for 16 h. After 16 h the reaction was quenched with EtOAc (4 mL) and water (2 mL). The organic layer was collected, dried over $MgSO_4$ and concentrated gently on a rotary evaporator at 40 °C. An aliquot was diluted in deuterated chloroform and analysed by GC and ^{1}H NMR to determine conversion and selectivity.

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