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New Arylaziridinyldifluoroborates: Useful Suzuki–Miyaura Reagents

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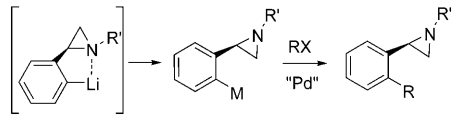
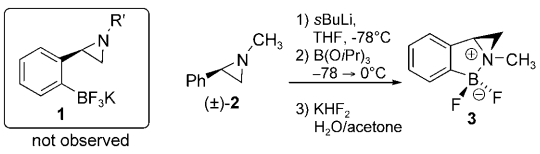
The directed *ortho*-metalation/cross-coupling strategy is an important synthetic tool for the preparation of biaryls, heterobiaryls and useful functionalized aromatic and heteroaromatic molecules.[1] Related synthetic applications are normally based on a one-pot procedure involving the generation of the suitable metalated intermediate followed by the coupling reaction.[2] Most of the organometallic partners needed for the cross-coupling reaction are usually prepared from organolithium or Grignard reagents by transmetalation with tin, zinc, indium or boron derivatives.[3,4] Within this methodology, although the one-pot protocol is undoubtedly advantageous in planning a synthetic process, in order to find the best reaction conditions (e.g., effective catalyst, ligand, solvent, co-catalyst or additive), it is often much better to be able to handle the organometallic or organometalloid partner separately. In this context, we envisaged that *ortho*-lithiated arylaziridines, recently investigated in our laboratory,[5] could be used for the preparation of new stable organometallic derivatives, useful, on the other hand, for the direct introduction of the aziridine moiety by the cross-coupling strategy. Among the organometallic coupling partners, several possibilities could be envisaged as depicted in Scheme 1.

The organotrifluoroborates are by far the most versatile because of their low toxicity, high-shelf stability, ease of preparation and the precise stoichiometry.[6] In particular, aziridine-functionalized organotrifluoroborates have not been described thus far. We are pleased to report that a new aziridinylaryldifluoroborate (**3**) has been prepared by *ortho*-lithiation of *N*-methyl-2-phenylaziridine (**2**), subsequent reaction with $B(OiPr)_3$ and treatment with aqueous KHF_2 (Scheme 2). After washing with acetone and solvent removal, a white powder was obtained containing not the expected trifluoroborate salt **1**, according to a reported protocol,[7] but the cyclic derivative **3** in nearly quantitative yield. It was nice to find that **3** could be easily obtained in multigram quantity and purified by chromatography on silica gel (85% isolated yield).[8]



Scheme 1. Directed *ortho*-metalation/cross-coupling strategy using aryl aziridines. Suzuki–Miyaura reactions: M = BR_2, shelf stability, water compatible. Negishi reactions: M = ZnX, in situ preparation, moisture sensitive. Corriu–Kumada: M = MgX, air and water sensitive, not suitable for storage. Stille reactions: M = SnR_3, toxic reagents, byproducts.



Scheme 2. Synthesis of cyclic difluoroborate **3**.

The structure of **3** was established on the basis of ^{1}H, ^{13}C, ^{11}B and ^{19}F NMR analysis (Figure 1). The ^{11}B NMR spectra showed a triplet at 8.0 ppm typical of a tetracoordinated boron atom ($^{1}J_{B-F}$ of 55 Hz) and the ^{19}F NMR showed two identical signals belonging to two diastereotopic fluorine atoms as proved by ^{19}F COSY experiment. The *ipso* carbon (C*i*) and the *N*-methyl group at δ = 141.3 and 38.5 ppm, respectively, were split for a ^{3}J coupling with the fluorine groups on the boron atom. It is worth noting that the ^{13}C–^{19}F coupling observed for the *N*-methyl group is an additional proof of the N–B interaction.[9] ^{19}F–^{11}B HMQC hetero-correlated experiment and 1D-NOESY further confirmed the structure of the difluoroborate and its cyclic nature (Figure 1).[10]

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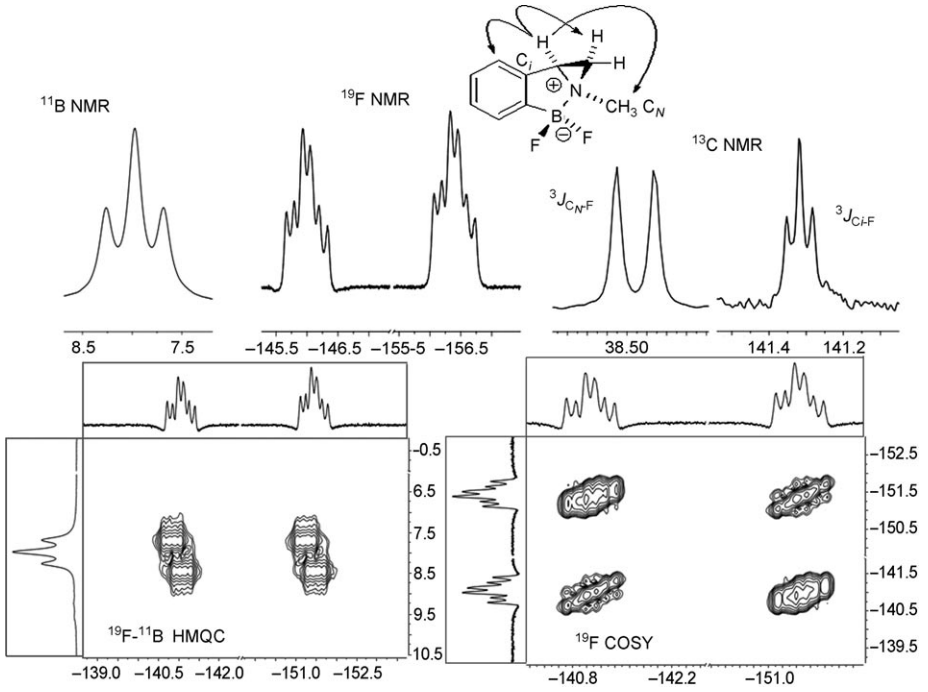


Figure 1. Multinuclear magnetic resonance analysis of difluoroborate **3** (selected NOE interactions shown).

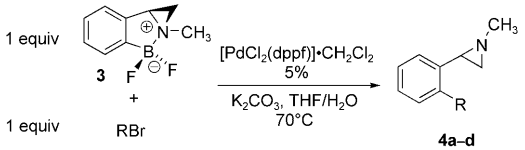
The difluoroborate **3** was found to be very stable under air and moisture and could be stored for months on the shelf. Preliminary stability tests showed that this derivative is stable under neutral and acidic conditions while it is sensitive to basic conditions suggesting that it could be considered as a masked form of a boronic acid.[11] In order to confirm this hypothesis, the reactivity of **3** was verified in Suzuki–Miyaura coupling reactions obtaining the results summarized in Table 1.

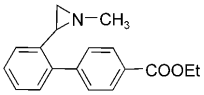
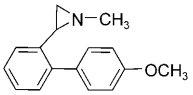
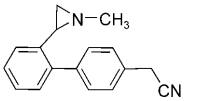
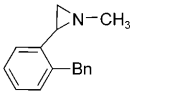
It was found that **3** gave cross-coupling reactions with aryl or benzyl bromides by using 5% $[PdCl_2(dppf)]\cdot CH_2Cl_2$ as the catalyst, K_2CO_3 as the base and a mixture of THF/H_2O as reaction solvent. Difluoroborate **3** could be *ortho*-arylated with good yields regardless of the electronic nature of the substituent on the aromatic bromide and also smoothly benzylated giving access to interesting *ortho*-functionalized aziridines **4a–d** that are not easily obtainable by other routes.[12]

The double functionalization was also investigated with the aim to obtain π-conjugated units with two aziridine moieties potentially useful as a fluorescent probe or ligands.[13] As can be seen in Table 2, the coupling reaction of **3** with aryl dibromides gave a mixture of mono- and bis-functionalized products, which, however, were easily separated by flash chromatography and fully characterized.[14]

This strategy represents a new approach to this kind of bis-functionalized aziridines and proves the usefulness of difluoroborate **3** as a new Suzuki–Miyaura reagent.

Table 1. Suzuki–Miyaura reactions of **3** with aryl bromides.



Product **4**	Yield [%][a,b]	Product **4**	Yield [%][a,b]
	64 (**4a**)		65 (**4c**)
	57 (**4b**)		70 (**4d**)

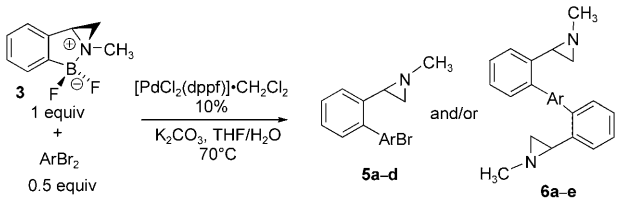
[a] Isolated yields. [b] Yields not optimized.

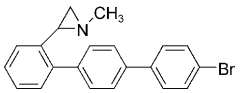
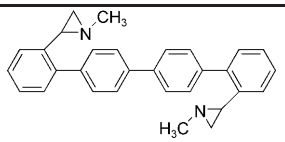
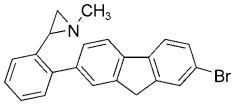
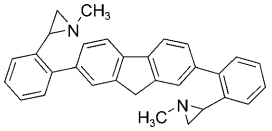
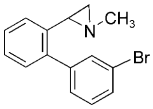
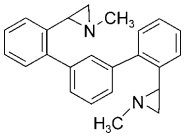
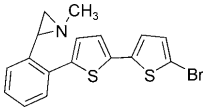
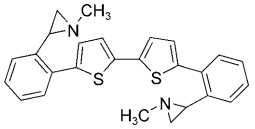
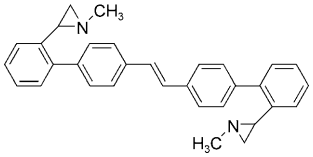
Concerning the stereochemistry of the bis-functionalized products **6a–e**, it is worth pointing out that the use of racemic difluoroborate **3** produces a mixture of two inseparable diastereoisomers which were undistinguishable by ^{1}H and ^{13}C NMR analysis. Only chiral HPLC analysis revealed the presence of two enantiomers and a *meso* form (see Supporting Information) in a 1:1 ratio. In order to set up an enantioselective synthesis of bis-functionalized derivatives of **6**, the enantioenriched difluoroborate (*S*)-**3** was prepared from the readily available chiral aziridine (*S*)-**2**[15] and cross-coupled with 4,4′-dibromobiphenyl, 2,7-dibromo-9*H*-fluorene obtaining the π-conjugated bis-aziridine (*S*,*S*)-**6a**,**b** highly enantioenriched. Coupling of (*S*)-**3** with ethyl *p*-bromobenzoate gave *ortho*-arylated aziridine (*S*)-**4a** also as single enantiomer (Scheme 3).

The preparation of optically active aziridinylaryldifluoroborates was successively pursued. Chiral difluoroborate (*S*,*S*)-**8** was prepared following the lithiation/boronation sequence on chiral aziridine (*S*,*S*)-**7** (Scheme 3).[16] (*S*,*S*)-**8**[17] was isolated by flash chromatography, fully characterized by NMR (see Supporting Information), in order to demonstrate the presence of the intramolecular N–B interaction, and used in a test cross-coupling reaction with ethyl *p*-bromobenzoate, to give the derivative (*S*,*S*)-**9** in good yields and highly enantioenriched.

The results described above, jointly to other literature examples,[18] seem to highlight that the benzylic nitrogen atom is prone to undergo intramolecular N–B interactions with the boron atom on the *ortho* position of the aromatic ring. In order to further verify this hypothesis and expand on the number of *ortho*-functionalized organodifluoroborates,

Table 2. Suzuki–Miyaura reactions of **3** with aryl dibromides.

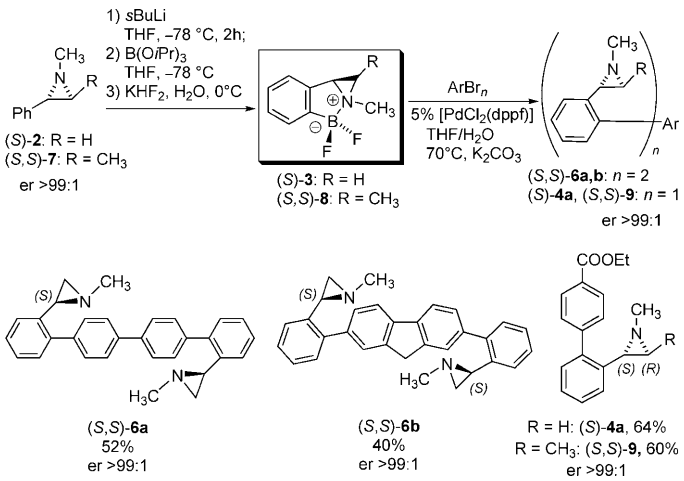


Product **5**[b]	Yield [%][a]	Product **6**[b,c]	Yield [%][a]
	14 (**5a**)		52 (**6a**)
	18 (**5b**)		40 (**6b**)
	22 (**5c**)		28 (**6c**)
	7 (**5d**)		23 (**6d**)
–	–		45 (**6e**)

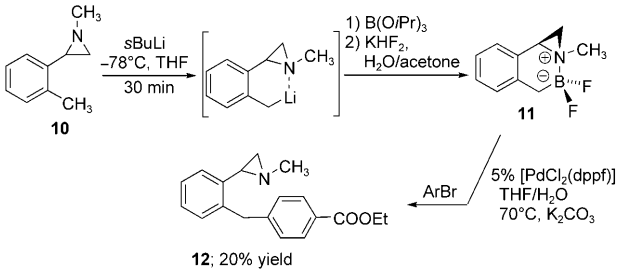
[a] Isolated yields. [b] Yields not optimized. [c] Inseparable mixture of two diastereoisomers was obtained (see main text).

which can serve as masked boronic acid derivatives, the lithiation/boronation sequence was executed on *o*-tolylaziridine **10** (Scheme 4). Lithiation occurred regioselectively at the lateral position[19] and subsequent reaction with $B(OiPr)_3$ and KHF_2 gave the difluoroborate **11** exclusively in 90% yield as a shelf-stable colorless oil that could be purified by flash chromatography.

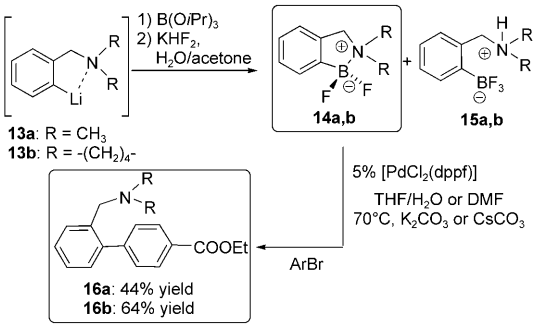
The intramolecular B–N interaction of difluoroborate **11** was established by multinuclear (^{19}F,^{11}B, ^{13}C, ^{1}H) magnetic resonance analysis and 1D-NOESY experiments (see Supporting Information). The difluoroborate **11** was then tested in a cross-coupling reaction with ethyl *p*-bromobenzoate obtaining the functionalized derivative **12** (20% isolated yield). For sake of comparison, the reactivity of *ortho*-lithiated benzylamines **13a**,**b** was investigated. The lithiated derivatives were generated as reported[20] and were subjected to boronation reaction obtaining a mixture of difluoroborates **14a**,**b** and trifluoroborate **15a**,**b** (Scheme 5) in a ratio **14a**/**15a** of 1:0.6 (93% overall yield) and **14b**/**15b** of 1:0.16 (70% overall yield) as confirmed by NMR analysis of the crude reaction mixture.[21] Flash chromatography (petroleum ether/AcOEt 1:1) of this mixture, furnished nearly pure difluoroborates **14a**,**b** (ca. 30% isolated yield) which were fully characterized by NMR analysis (see Supporting Information). It is likely that the higher degree of freedom of these benzylic derivatives and steric effects[22] favor the presence of the acyclic trifluoroborate which was never observed with more constrained aziridines. The reason of this different behavior is currently under investigation. However, difluoroborates **14a**,**b** were prone to undergo palladium-catalyzed cross-coupling reactions giving the *ortho*-functionalized benzyl amines **16a**,**b** (Scheme 5).



Scheme 3. Synthesis of enantioenriched π-conjugated bis-aziridines **6a**,**b**.



Scheme 4. Synthesis and reaction of difluoroborate **11**.



Scheme 5. Synthesis and reactions of organoboron derivatives **14** and **15**.

In summary, this work describes the preparation of new shelf-stable aziridinyldifluoroborates even in enantioenriched form that can serve either as Suzuki–Miyaura reagents and as new bifunctional Lewis pairs potentially useful as catalysts or tweezers for small-molecule binding.[23] Such thus far undescribed aziridinedifluoroborates, which can be used for the *ortho*-functionalization of aromatic aziridines, are, to the best of our knowledge, the first examples of aziridine-functionalized cross-coupling reagents. The methodology could be expanded to other benzylamine derivatives and aryl-substituted *N*-heterocycles in order to obtain new shelf-stable organoboron reagents. More work is underway in our laboratory in order to expand the synthetic utility of these new reagents.

Experimental Section

General procedure for Suzuki–Miyaura cross-coupling reactions: To a degassed solution of aziridinedifluoroborate **3** (127 mg, 0.7 mmol) in THF/H_2O 10:1 (10 mL) were added K_2CO_3 (290 mg, 2.1 mmol), aryl halide (0,7 mmol) and $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (28 mg, 0.035 mmol). The reaction mixture was stirred at 70°C, until aryl halide had been completely consumed as determined by TLC or GC-MS. The reaction mixture was allowed to cool to RT and diluted with water followed by extraction with Et_2O. The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography to yield the pure product.

Acknowledgements

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Keywords: aziridines · C–C coupling · directed lithiation · NMR spectroscopy · organoboron reagents

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[14] Attempts to improve yields and selectivity reported in Table 1 and 2 gave unsatisfactory results. Varied conditions were investigated with reference to reaction solvent, ligand, Pd source, base.
[15] Chiral aziridine (*S*)-**2** has been prepared starting from commercially available (*S*)-styreneoxide by a ring-opening–ring-closing sequence according to reported procedures, see: a) J. R. Pfister, *Synthesis* **1984**, 969–970; b) W. K. Anderson, A. S. Milowsky, *J. Med. Chem.* **1986**, *29*, 2241–2249; c) S. Fujita, K. Imamura, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1975–1977.
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