

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
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TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 7
ACT: 430 REQUERSOLICITA	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
LUZ CLEMENCIA DE PÁEZ

Asunto: Radicación: 14-158850- -2
 Trámite: 11
 Evento: 378
 Actuación: 430
 Oficio: 12256
 Folios: 7

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	pct/us2012/070967				
Fecha de Presentación Internacional	20/12/2012				

1. Documentos estudiados

Descripción:	Rad 14-158850-00000-0000	22/julio/2014
Reivindicaciones:	Rad 14-158850-00000-0000	22/julio/2014
Prioridad:	Rad 14-158850-00000-0000	22/julio/2014
US 61/582,173 30/12/2011		

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque ésta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del capítulo primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada. En este caso se encuentra el pago adicional de la tasa que cubre 11 reivindicaciones adicionales, de tal forma que se estudiará el capítulo reivindicatorio completo.

Título de la solicitud: Métodos de formación de ésteres pinacólicos de ácido 4-cloro-2-fluoro-3-sustituido-fenilborónico y sus métodos de uso. Folio 1.

Objeto de la invención: El objeto de la presente solicitud de patente de invención se refiere a un método para formar un éster pinacólico de ácido 4-cloro-2-fluoro-3-sustituido-fenilborónico.

El problema técnico planteado en la presente solicitud de patente se refiere a la necesidad de disponer de un éster de ácido 4-cloro-2-fluoro-3-sustituido-fenilborónico que tenga un punto de fusión relativamente mayor y que se pueda formar eficazmente y usar eficientemente en procesos posteriores, como la producción de intermediarios herbicidas. Para solucionar ese problema técnico la presente solicitud plantea un método para formar un éster pinacólico de ácido 4-cloro-2-fluoro-3-sustituido-fenilborónico.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07B61/00; C07F5/02.

4. De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

El capítulo reivindicatorio no cumple con el requisito de concisión y además se considera una generalización que no se encuentra enteramente soportada en la descripción, dadas las múltiples posibilidades descritas en la reivindicación 1. El solicitante debe definir específicamente la materia y el alcance de la invención a través de las características técnicas esenciales que se encuentren enteramente soportadas en la descripción, sírvase limitar el alcance de la invención.

Se llama la atención de la solicitante frente a las reivindicaciones 2, 10, 19 y 21, las cuales presentan el rendimiento de la reacción como característica técnica esencial del método. No obstante, en el lenguaje de patentes no es aceptable que el rendimiento sea característica técnica esencial del método de síntesis, toda vez que consiste en un resultado a alcanzar. Sírvase suprimir dichas reivindicaciones y definir el método de interés por medio de sus etapas de proceso y condiciones de ejecución, específicamente definidas.

Asimismo sírvase suprimir los términos “*al menos, aproximadamente, mayor o igual, más ó igual*” puesto que son ambiguos y no permiten definir específicamente el objeto de invención.

Finalmente sírvase corregir la reivindicación 16, suprimiendo la referencia “de uso” dado que genera confusión y pareciera que se refiere a una reivindicación de uso y no de método.

En consecuencia, el capítulo reivindicatorio no cumple con el requisito de concisión, claridad y sustento en la descripción de acuerdo al art. 30 de la Decisión 486.

5. Determinación del Estado de la Técnica

Considerando que la fecha de la solicitud de prioridad es 30 de diciembre de 2011 se realizó la búsqueda en el estado de la técnica y se encontraron los documentos relacionados a continuación que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
D1	US 7611647	Process for the selective deprotonation and functionalization of 1-fluoro-2-substituted-3-chlorobenzenes	3-11-2009
D2	Cambridge	Application of the Suzuki Reaction as the Key Step in the Synthesis of a Novel Atropisomeric Biphenyl Derivative for Use as a Liquid Crystal Dopant	Received May 15, 2003
D3	Harwig	Synthesis and characterization of 2,6-difluoro-4-carboxyphenylboronic acid and a biotin derivative thereof as captors of anionic aqueous[18F]-fluoride for the preparation of [18F/19F]-labeled aryltrifluoroborates with high kinetic stability.	Available online 8 March 2008 Abstract

El solicitante podrá consultar el documento citado en la siguiente dirección URL:
<https://register.epo.org/application?number=EP12862457&tab=main>

El documento D1 divulga un proceso selectivo de deprotonación y funcionalización del 1-fluoro- 3-clorobenzenos-2-substituidos.

El documento D2 hace referencia a aplicaciones de la reacción de Suzuki

El documento D3 hace referencia a la síntesis y caracterización del ácido 2,6-difluoro-4-carboxifenilborónico.

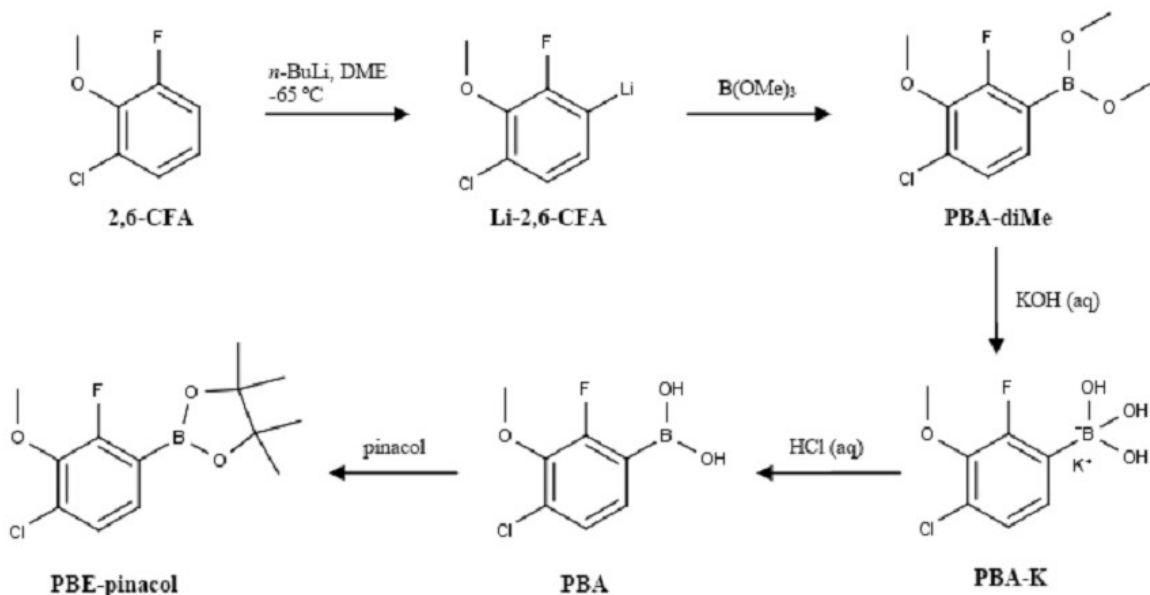
6 . Examen de patentabilidad (artículo 14 D486)

Nivel Inventivo (artículo18 D486)

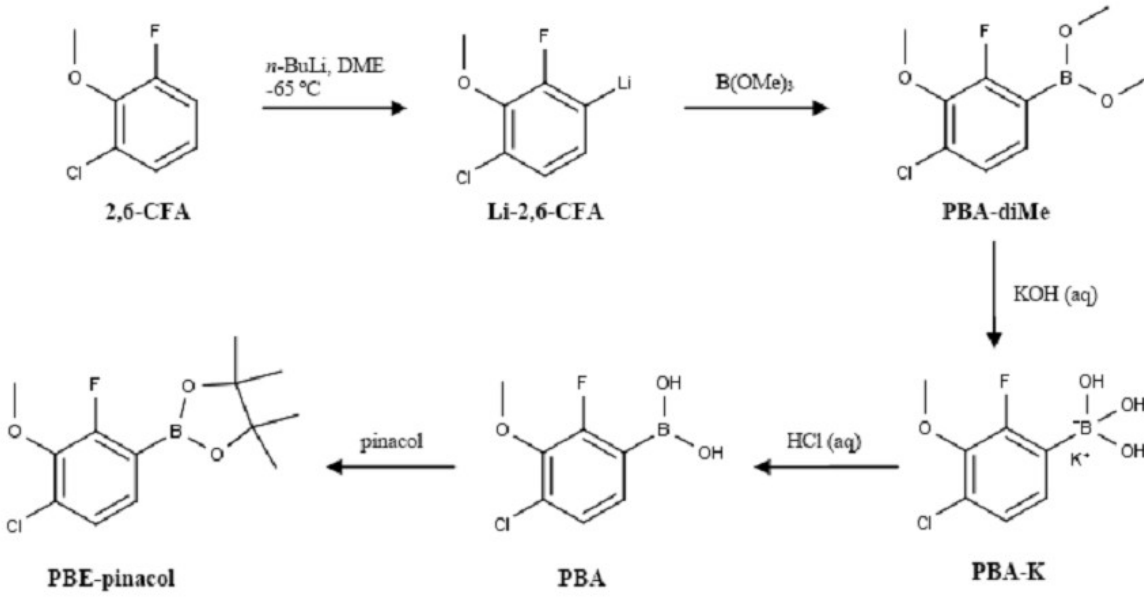
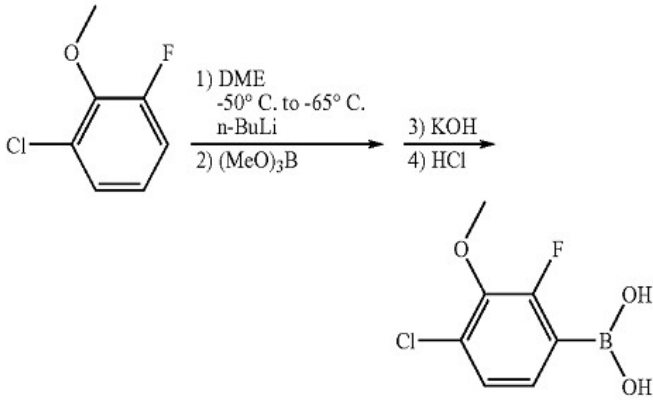
La reivindicación 1 divulga un método para formar un éster pinacólico de ácido 4–cloro–2–fluoro–3–sustituido–fenilborónico, que comprende:

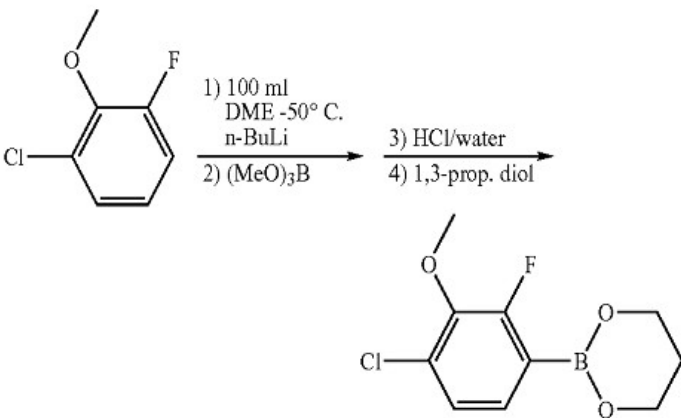
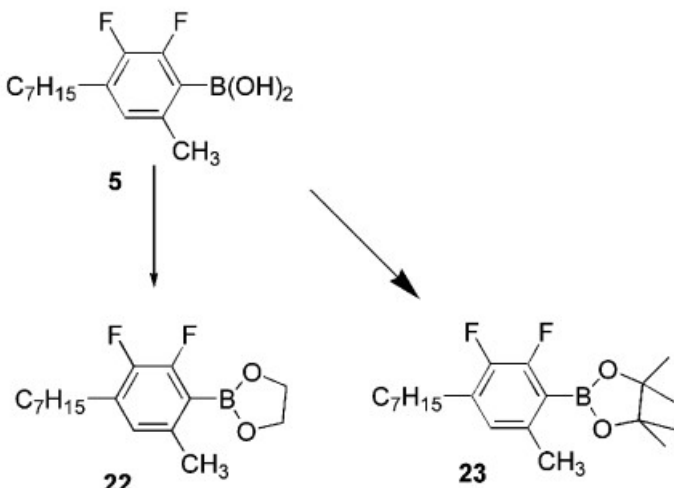
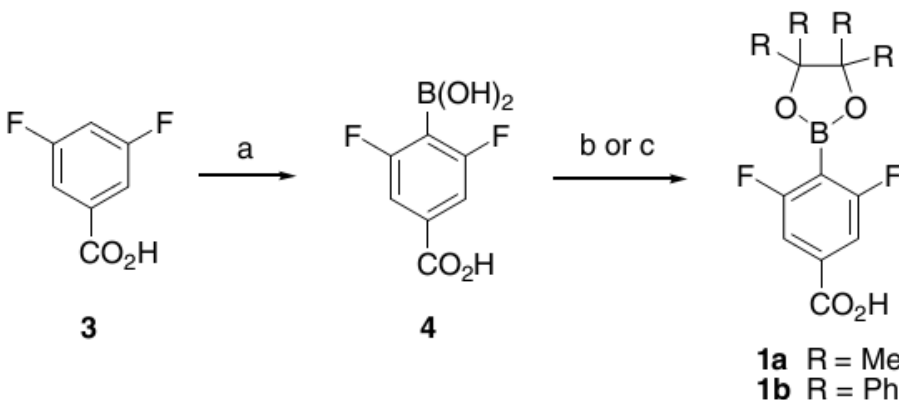
- o poner en contacto un 1–cloro–3–fluoro–2–sustituido–benceno con un alquil-litio para formar un 1–cloro–3–fluoro–2–sustituido–benceno litiado;
- o poner en contacto el 1–cloro–3–fluoro–2–sustituido–benceno litiado con un derivado de ácido borónico electrofílico para formar un 4–cloro–2–fluoro–3–sustituido–fenilboronato;
- o hacer reaccionar el 4–cloro–2–fluoro–3–sustituido–fenilboronato con una base acuosa para formar un (4–cloro–2–fluoro–3–sustituido–fenil)trihidroxiborato;
- o hacer reaccionar el (4–cloro–2–fluoro–3–sustituido–fenil)trihidroxiborato con un ácido para formar un ácido 4–cloro–2–fluoro–3–sustituido–fenilborónico; y
- o hacer reaccionar el ácido 4–cloro–2–fluoro–3–sustituido–fenilborónico con 2,3–dimetil–2,3–butanodiol.

Ver radicado 14-158850-00000-0000.



La siguiente tabla presenta la comparación entre las características técnicas esenciales de la solicitud estudiada, mencionadas en la reivindicación 1 y las reveladas en el estado de la técnica.

Solicitud	 The reaction scheme shows the synthesis of PBE-pinacol from 2,6-CFA (2-chloro-6-fluorophenyl methyl ether). The steps are as follows: 2,6-CFA reacts with $n\text{-BuLi}$ in DME at -65°C to form Li-2,6-CFA (lithium 2-chloro-6-fluorophenyl methyl ether). - Li-2,6-CFA reacts with B(OMe)_3 to form PBA-diMe (dimethyl 2-chloro-6-fluorophenyl borate). - PBA-diMe reacts with KOH (aq) to form PBA-K (potassium 2-chloro-6-fluorophenyl borate). - PBA-K reacts with HCl (aq) to form PBA (2-chloro-6-fluorophenyl boronic acid). - PBA reacts with pinacol to form PBE-pinacol (pinacolato 2-chloro-6-fluorophenyl borate).
D1	 The reaction scheme shows the synthesis of PBA (2-chloro-6-fluorophenyl boronic acid) from 2,6-CFA (2-chloro-6-fluorophenyl methyl ether). The steps are as follows: 2,6-CFA reacts with 1) DME, -50°C to -65°C, $n\text{-BuLi}$ and 2) $(\text{MeO})_3\text{B}$ to form PBA-diMe (dimethyl 2-chloro-6-fluorophenyl borate). - PBA-diMe reacts with 3) KOH and 4) HCl to form PBA (2-chloro-6-fluorophenyl boronic acid).

	
D2	
D3	 Scheme 1. Reagents and conditions: (a) <i>sec</i>-BuLi, TMEDA, THF, -78°C then $\text{B}(\text{OMe})_3$ then HCl, 75%; (b) R = Me, pinacol, THF/PhMe, 40°C, quant.; (c) R = Ph, benzopinacol, THF/PhMe, reflux, 72%.

Los documentos D1 a D3 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque:

El documento D1 ya había dado a conocer un método para formar un éster de ácido 4-cloro-2-fluoro-3-sustituido-fenilborónico, ver esquema de reacción, tabla anterior.

La diferencia entonces entre el método de la reivindicación 1 y el método del documento D1 radica en que no se hace referencia a la etapa de hacer reaccionar el

ácido 4-cloro-2-fluoro-3-sustituido-fenilborónico con 2,3-dimetil-2,3-butanodiol, ver ejemplo 2.

No obstante, no se observa ningún efecto técnico debido a dicha diferencia dado que se siguen obteniendo esteres pinacólicos de ácido 4-cloro-2-fluoro-3-sustituido-fenilborónico con buena eficiencia y alta pureza.

De este modo, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: ¿cómo tener un método para la síntesis de esteres pinacólicos de ácido 4-cloro-2-fluoro-3-sustituido-fenilborónico alternativo?

Sin embargo, la esterificación de ácidos borónicos es ampliamente conocida en estado del arte, incluso el mismo documento D1 divulga la obtención del éster correspondiente por reacción un compuesto diol, el 1,3 propanodiol.

Pero además, los documentos D2 o D3 también hacen referencia a la esterificación de ácidos borónicos por reacción con dioles.

El documento D2 por ejemplo, divulga la reacción de esterificación de un ácido borónico con un compuesto diol como el pinacol, (página 6833 y esquema 3)

El documento D3 por su parte, divulga la reacción de esterificación de un ácido borónico con un compuesto diol como el pinacol, (esquema 1)

De esta forma, la persona del oficio medianamente versada en la materia, tiene información suficiente a partir de la combinación de enseñanzas de los documentos D1 y D2 o D1 y D3 para derivar de forma obvia el método de la presente solicitud con la plena expectativa de éxito en cuento a obtener un éster de ácido 4-cloro-2-fluoro-3-sustituido-fenilborónico, con alta eficiencia, pureza y estabilidad.

En consecuencia la materia objeto de la presente solicitud, se deriva de manera evidente del arte previo, no provoca ningún efecto técnico sorprendente o inesperado y carece de nivel inventivo. De forma análoga, el método de las reivindicaciones 9 y 16, sus dependientes, y el compuesto de la reivindicación 21 tampoco son inventivos.

Se reitera que la solicitud no demostró ningún efecto técnico inesperado o sorprendente que pueda entenderse como un salto cualitativo a la regla técnica.

7. Conclusión

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US 7611647	1-21	Nivel Inventivo
D2	Cambridge	1-21	Nivel Inventivo
D3	Harwig	1-21	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2015-10-20

Elaboró: Sandra Isabel Calderon Rodriguez
Revisó: Rubiela Pacanchique Vargas

Application of the Suzuki Reaction as the Key Step in the Synthesis of a Novel Atropisomeric Biphenyl Derivative for Use as a Liquid Crystal Dopant

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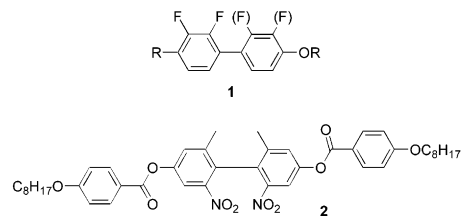
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Received May 15, 2003

Abstract: A heavily functionalized atropisomeric biphenyl derivative (**4**), which is designed to possess a large lateral dipole moment, has been synthesized with use of a Suzuki coupling as the key step and resolved by chiral HPLC. The final coupling reaction is complicated by rapid hydrolytic deboronation of the sterically hindered, electron poor boronate **22**. Rigorously anhydrous conditions are therefore necessary to achieve the coupling.

Restricted rotation around the aryl–aryl bond in biaryls can lead to the phenomenon of atropisomerism (sometimes referred to as helical chirality). The chiral biaryl motif is encountered in some natural products¹ but is most commonly exploited in the field of asymmetric synthesis² where derivatives of, for example, binaphthalene find widespread use. The biphenyl unit itself is commonly encountered as a core in the liquid crystal field where derivatives have found commercial application (most notably in displays).^{3,4} Fast switching ferroelectric display devices require a smectic liquid crystal that is chiral and exhibits a room-temperature chiral smectic C phase. Furthermore, to switch the device the molecules must possess a significant lateral dipole moment. In real systems this is most commonly achieved by using mixtures whereby a host liquid crystal is “doped” with a chiral additive. For maximum effect (induction of high spontaneous polarization with minimal disruption of liquid crystal properties) the stereopolar unit (which includes the chiral center and all coupled polar functional groups contributing to a transverse molecular dipole) should be as close as possible to the core. Furthermore, to ensure compatibility the dopant structure should ideally bear close resemblance to the hosts (for example polyfluorobiphenyls such as **1**⁵).



With the above criteria in mind it is clear that atropisomeric biphenyls could fulfill the role of ideal dopants for smectic liquid crystals leading to chiral smectic C phases. Indeed the first examples of such materials have been reported recently by Lemieux,⁶ who prepared derivatives of 4,4'-dihydroxy-2,2'-dimethyl-6,6'-dinitrobiphenyl such as **2**. The materials (resolved by chiral HPLC) were not liquid crystalline but were capable of inducing spontaneous polarization when doped into host materials.

One of the most useful and versatile methods for synthesizing biaryls is the Suzuki reaction⁷ whereby an arylboronic acid (or derivative) is coupled with an aryl halide (for example) under palladium catalysis. The reactions generally work well for simple substrates but problems are often encountered when sterically hindered partners are employed.^{8,9} We recently reported¹⁰ the first examples of intermolecular asymmetric Suzuki reactions¹¹ leading to atropisomeric binaphthalenes in reasonable yields and ee values, and further examples have since appeared.¹² We reasoned that the Suzuki reaction could be employed as the key step in the synthesis of dipolar, unsymmetrical biphenyls for use as liquid crystal dopants, and that the asymmetric modification would lead to enantiomerically enriched material.

In this paper we report the synthesis of a heavily functionalized biphenyl derivative **4**. The choice of **4** as a target molecule stems from the design criteria set out above. A typical smectic C liquid crystal host material is difluorobiphenyl **3**.⁵ Elaboration of this structure to give a molecule with sufficient hindrance to prevent racemization and bear a lateral dipole moment yields structure **4** (by definition the chiral center of such atropisomers is on the core). Fluoride and nitrile substituents were chosen to induce the dipole moment because of their compatibility with use in liquid crystal devices. Apolar (methyl) groups were chosen to occupy the 6,6'-positions.

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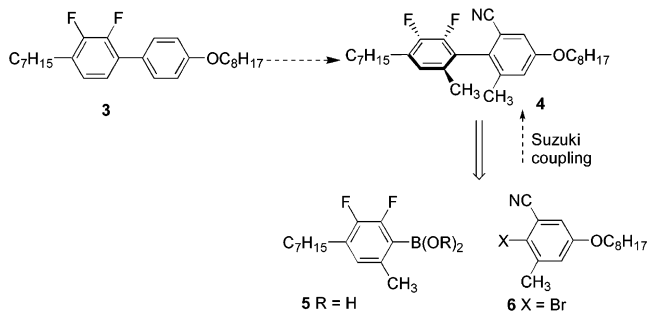
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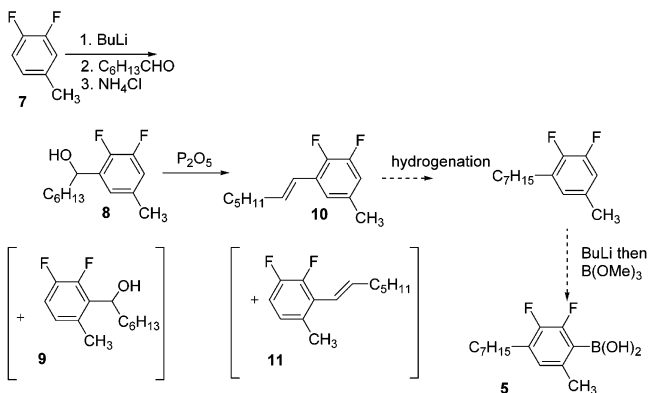
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SCHEME 1. Molecular and Synthetic Design of Target Biphenyl 4



SCHEME 2. Planned Synthesis of Boronic Acid 5



Simple molecular modeling (Hyperchem-AM1) and calculation of interference values¹³ led to the prediction that **4** would be stable to racemization even at elevated temperatures.

The key disconnection for our synthesis is also shown in Scheme 1. It was envisaged that boronic acid **5** would be easily synthesized from commercially available 3,4-difluorotoluene **7** according to Scheme 2. **7** was therefore ortho-lithiated with butyllithium at $-78\text{ }^{\circ}\text{C}$ and quenched with heptanal. Analysis of the crude product clearly indicated that a mixture of regioisomeric alcohols **8** and **9** had been formed in a ratio of 8:3. This mixture proved impossible to separate by chromatography and modification of the reaction conditions to favor exclusive formation of the desired regioisomer **8** (lower temperature, *t*-BuLi) led to no improvement. The isomeric mixture was therefore dehydrated (phosphorus pentoxide) but again the resulting mixture of regioisomeric alkenes proved inseparable.

Boronic acid **5** and its corresponding pinacol ester **22** were eventually synthesized from difluorobenzene itself according to Scheme 3. 1,2-Difluoro-3-heptylbenzene was synthesized via ortho-lithiation following the reported procedure.^{5b} Direct electrophilic halogenation of **13** was not possible (it resulted only in formation of **14**) so a second ortho-lithiation was employed and the resulting aryllithium intermediate was quenched with iodine giving **15**. Treatment of **15** with methoxyacetyl chloride/tin chloride at room temperature resulted in slow chloromethylation with the desired regioisomer being produced

as a minor product. An activating (directing) methoxy group was therefore introduced by displacing the iodide by treatment with sodium methoxide and catalytic copper(I) iodide¹⁴ giving **18**. This reaction resulted in some reduced product **13**, which was recycled. Chloromethylation of **18** successfully yielded the correct regioisomer. However, it proved most convenient to introduce the methyl group directly via a further ortho-lithiation. Consequently anisole **18** was treated with butyllithium in cyclohexane/THF¹⁵ and then quenched with methyl iodide to afford **19**. The use of carefully controlled conditions reduced the formation of a side product resulting from displacement of one fluoride by butyllithium. Hydrolysis of **19** produced the phenol, which was deoxygenated via triflate **20** to give **21**.¹⁶ The target boronic acid **5** was prepared in modest yield (42%) by a further ortho-lithiation of **21** followed by reaction with trimethylborate and aqueous workup. Significant quantities (30%) of unreacted starting material were isolated from this reaction. The corresponding boronate esters **22** and **23** were prepared by reaction of **5** with the appropriate diol. It is worth noting that direct synthesis of pinacol boronate **23** from triflate **20** was attempted with Masuda's conditions¹⁷ but resulted in no reaction.

Coupling partner **6** was synthesized following the route shown in Scheme 4, using a statistical desymmetrization as the key step. 3,5-Dimethylphenol was brominated with molecular bromine in acetic acid¹⁸ and the resulting bromide **25** was smoothly alkylated to give symmetrical intermediate **26**. Benzylic bromination of **26** was achieved with use of NBS and catalytic benzoyl peroxide under irradiation by a 150-W tungsten lamp. By using this method, dibromide **27** could be obtained in a yield of 45%. A number of standard methods were employed for the conversion of benzyl bromide **27** into the corresponding amine **28**. It proved most efficient to use a two-step procedure whereby the azide was prepared and subsequently reduced with lithium aluminum hydride affording an overall yield of about 80%.¹⁹ Oxidative dehydrogenation of **28** proved troublesome. Standard conditions employing nickel peroxide²⁰ or sodium hypochlorite²¹ resulted in the formation of large amounts of aldehyde (from hydrolysis of the intermediate imine). The best conditions involved the use of copper(I) chloride/oxygen in dry pyridine in the presence of molecular sieves²² and yields of over 80% were possible.

Initial attempts at Suzuki coupling reactions between boronic acid **5** and bromide **6** were performed with either

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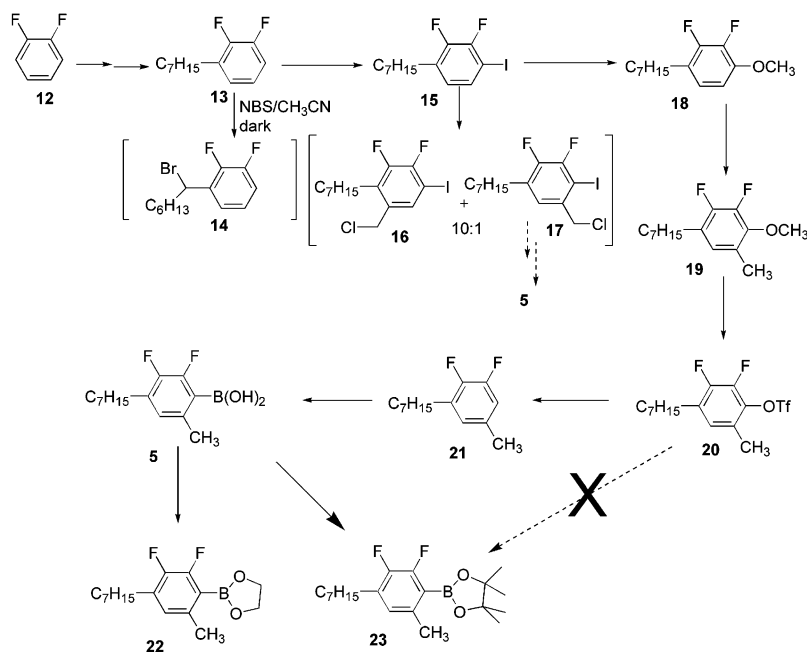
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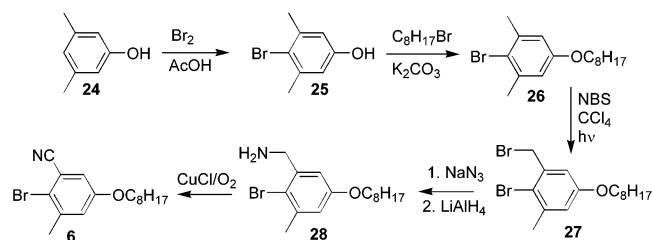
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SCHEME 3. Synthesis of Boronic Acid 5 and Corresponding Boronate Esters

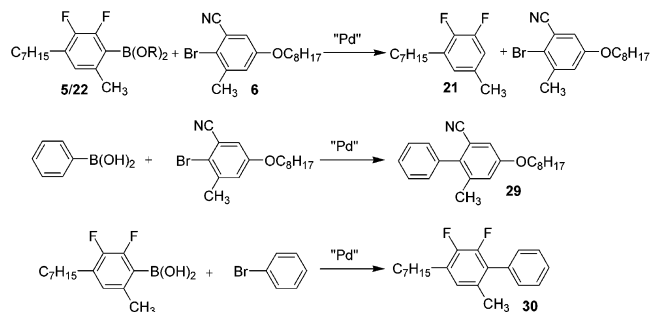


SCHEME 4. Synthesis of 6



preformed $\text{Pd}(\text{Ph}_3)_4$ or a catalyst prepared in situ from palladium chloride and 2 equiv of triphenyl phosphine under standard conditions. Not surprisingly, these conditions failed to produce any of the desired biphenyl and unreacted **6** was reisolated along with **21** (resulting from hydrolytic deboronation). It is well-known that deboronation tends to dominate in reactions of hindered boronic acids²³ and in our previous work on the asymmetric Suzuki coupling of hindered naphthalenes this problem was overcome by employing the boronate ester as a coupling partner.¹⁰ These (homogeneous) conditions were applied to the coupling of **6** with ester **22**. Unfortunately, the coupling reaction in either DME or THF with cesium fluoride gave essentially the same disappointing result, prompting a closer examination of the reaction to obtain information about the individual mechanistic steps. To this end, bromide **6** and boronic acid **5** were coupled with benzene boronic acid and bromobenzene respectively under standard conditions. In both cases the coupled product was smoothly obtained (albeit in modest unoptimized yields of around 40%), demonstrating that oxidative addition of **6** and transmetalation of **5** to palladium are facile. Further experiments were performed to test the susceptibility of **22** to deboronation. It was found that the rate of deboronation was dramatically accelerated by addition of palladium catalyst. In one control experiment **22** was stirred in

SCHEME 5. Attempted Suzuki Coupling To Give Target Biphenyl 4 and Model Couplings



dried dioxane with cesium fluoride at 100 °C under nitrogen. Deboronation was complete within 4 h. As expected use of carefully dried reagents and nitrogen slowed the deboronation considerably. When the original experiment was carried out in the presence of a catalytic quantity of palladium it was observed that deboronation was complete within minutes. Further control experiments demonstrated that formation of ate complexes is required to promote deboronation. For example, no deboronation was observed after 24 h when **22** was treated with Pd/C, triphenyl phosphine, and triethylamine in refluxing ethanol. Addition of cesium fluoride to the reaction mixture resulted in complete deboronation in under 2 h.

These observations permit some assumptions to be made about the limiting steps in this coupling process and they, along with the side reactions, are depicted in Figure 1. The overall rate-limiting step appears to be reductive elimination, itself likely to be driven by a further oxidative addition of **6** via a transition state such as **31**.²⁴ (This triggered reductive elimination is likely to account for the improvement in the coupling of sterically

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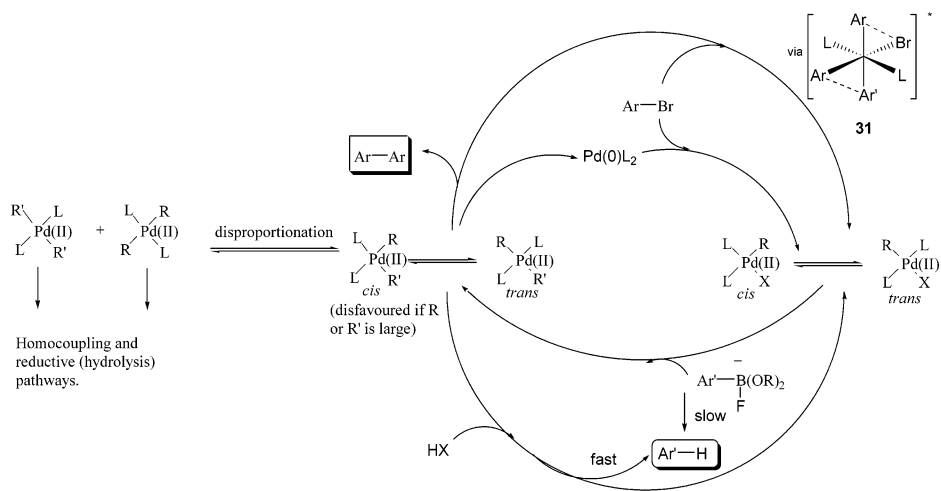
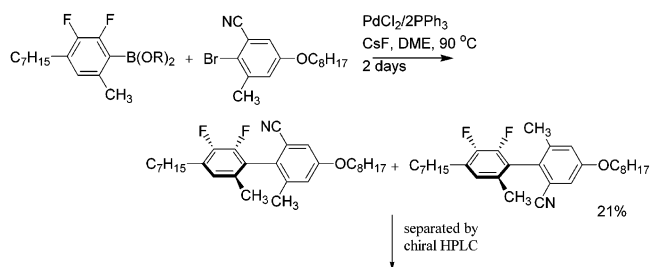


FIGURE 1. Catalytic cycle and side reactions.

hindered substrates when aryl iodides are used in place of bromides even in cases where it is known that the "simple" oxidative addition step is facile.) The reductive elimination can only occur from the cis-complex and the slow rate could equally plausibly stem from the unfavorable (for such hindered substrates) cis–trans equilibrium. These factors mean that the diaryl palladium species has a long lifetime and is susceptible to competing processes such as disproportionation and hydrolysis. The latter process clearly dominates in this case. Attempts to improve the reaction by choice of palladium source (such as PdCl_2 , $\text{Pd}(\text{OAc})_2$, $\text{Pd}_2(\text{dba})_3$), ligand (such as PPh_3 , dppf , dppe , $\text{P}(\text{OMe})_3$), solvent (such as DME, DMF, toluene, dioxane, THF), and base (K_3PO_4 , CsF) met with no success and in all cases hydrolytic deboronation dominated.

Successful coupling could only be achieved when the reaction was performed with rigorous exclusion of moisture.²⁵ To this end all reagents were dried under vacuum and handled under dried nitrogen. The reaction proved to be poorly reproducible but gave the target biphenyl **4** in a yield of up to 21% when PdCl₂ (3%)/PPh₃ (6%) was used as catalyst in DME with cesium fluoride at 90 °C for 2 days. Application of our previously established conditions for performing asymmetric Suzuki couplings failed to yield any biphenyl. A sample of (±)-**4** was, however, separated into its enantiomers by chiral HPLC to permit characterization of the pure compounds (which are oils).

In conclusion, a heavily functionalized biphenyl derivative has been synthesized with use of a Suzuki coupling



as the key step. As with other examples of attempts to couple sterically hindered partners, this reaction proved difficult to achieve with, in our case, hydrolytic deboronation dominating. Model experiments and a careful analysis of reaction conditions leads to the conclusion that the slow reaction step is reductive elimination (or the trans to cis isomerization required to give the intermediate capable of reductive elimination). Deboronation takes place in the absence of palladium but the reaction rate is dramatically accelerated with palladium present. This suggests that deboronation takes place from a diarylpalladium species, setting up a separate catalytic cycle that consumes the boronate. Coupling can only be achieved if the deboronation pathway can be stopped by rigorous exclusion of moisture.

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Supporting Information Available: Full experimental details and comparison of synthetic methods, NMR spectra, and HPLC. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(25) It is interesting to compare our results to those of Buchwald [ref 8], who reported that strictly anhydrous conditions were required to prevent destruction of the *bromide* coupling partner, an observation that further emphasizes the mechanistic balance required for successful coupling of hindered substrates.

Synthesis and characterization of 2,6-difluoro-4-carboxyphenylboronic acid and a biotin derivative thereof as captors of anionic aqueous [^{18}F]-fluoride for the preparation of [$^{18}\text{F}/^{19}\text{F}$]-labeled aryltrifluoroborates with high kinetic stability

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Abstract

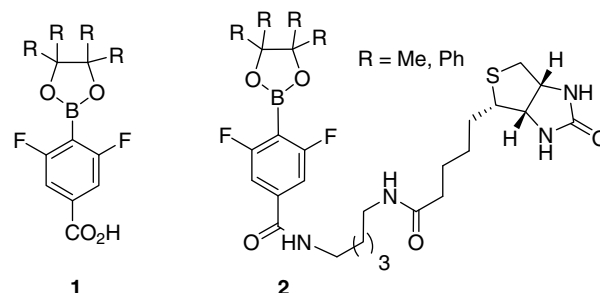
Arylboronic esters are readily converted to aryltrifluoroborates in the presence of aqueous fluoride. As such these represent attractive synthetic precursors that afford one-step labeling with [^{18}F]-fluoride for the generation of PET reagents. Herein we present the synthesis of a heretofore undisclosed arylboronic ester that is converted to its corresponding trifluoroborate. Essential for contemplating its use in PET imaging is the demonstration of kinetic resistance to solvolytic defluoridation.

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1. Introduction

Boronic acids have enjoyed widespread use, from serving as important building blocks for organic synthesis to acting as chemical sensors for carbohydrate recognition and components in pharmaceutically important enzyme inhibitors.¹ Their extensive use in synthetic and bioorganic chemistry led us to propose their use as precursors for the formation of PET (positron emission tomography) imaging agents based on their fluorophilicity for anionic [^{18}F]-fluoride to afford trifluoroborates with extraordinary chemo-selectivity.² This potential is highlighted in a preliminary investigation of 2,4,6-trifluoro-3-carboxamidophenylboronic ester as a captor of aqueous [^{18}F]-fluoride in the preparation of an [^{18}F]-labeled aryltrifluoroborate PET radiotracer.³ This particular electron-poor aryltrifluoroborate was discovered to be especially stable to solvolytic

defluoridation and it was hypothesized that the electron-deficiency contributed to its stability. Extending that hypothesis, herein we describe the synthesis of protected 2,6-difluoro-4-carboxyphenylboronic acid (**1**) as a second and perhaps equally attractive candidate precursor for [^{18}F]-capture, as well as its biotin conjugate (**2**) which was prepared to demonstrate further potential for biomolecule labeling. Compounds **1** and **2** are shown in the next column.



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2. Results and discussion

Due to the lack of a commercially available, suitably functionalized electron-poor arylboronic acid, the synthesis of the carboxy-substituted compound **4** was envisaged by metallation of 3,5-difluorobenzoic acid (**3**) (Scheme 1).

Lithiation of **3** with *sec*-BuLi (or *n*-BuLi) in THF in the presence of TMEDA at -78°C followed by trapping of the resultant dilithiated species with trimethylborate afforded 2,6-difluoro-4-carboxyphenylboronic acid **4** as the exclusive regioisomer⁴ in good yields on the gram scale.⁵ The boronic acid **4** was easily converted to the pinacol ester **1a**⁶ in quantitative yield.

Efforts were then undertaken to couple the pinacol ester **1a** to a biotinylated derivative for the preparation of a radiotracer precursor with affinity for avidin and fusion constructs thereof. To this end, the Boc-protected amino-linked biotin **5**⁷ was prepared and treated with TFA. The resultant TFA salt was then coupled to **1a** using standard EDC coupling conditions with DIPEA or triethylamine as base (Scheme 2).

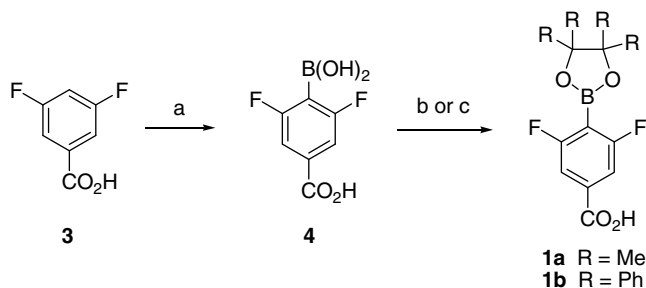
Under these conditions, a significant proportion of protodeboronated product **6** (~ 20 – 30% as determined by ^1H and ^{19}F NMR)⁸ was obtained and this decomposition byproduct could not be easily separated from the desired boronate ester adduct **2a** by standard silica chromatography. As a result, other coupling conditions and isolation methods were explored. The commercially available *N,N*-

diethanolaminomethyl polystyrene (DEAM-PS) resin⁹ was employed in an attempt to immobilize the boronic acid **4** onto a solid support. As expected for electron-poor arylboronic acids, a low yield of immobilization (44%) was obtained and, upon examination of the remaining unbound material, it was discovered that a significant portion had also undergone protolytic deboronation.¹⁰ Attempts to protect **2** with equimolar amounts of unbound *N*-methyl-diethanolamine gave similar results.¹¹ Although this phenomenon has not been well characterized in the literature, arylboronic acids containing strong electron-withdrawing groups are known to be susceptible to this type of deboronation under basic conditions.¹² Consequently, the coupling of **1a** with the biotin-linked amine was repeated using pyridine as a milder base to avoid the formation of **6**. Notably, this minor modification provided the desired biotinylated adduct¹³ cleanly in 60% yield with little formation of deboronated **6** ($<5\%$) as observed by ^1H and ^{19}F NMR.

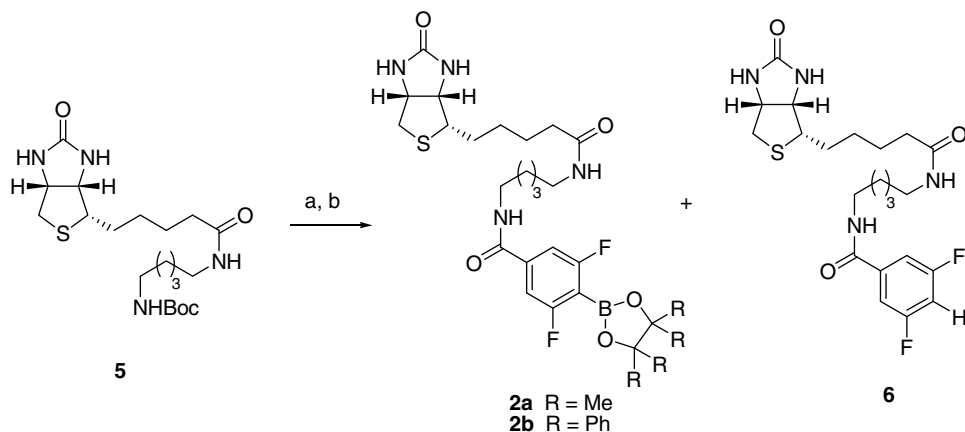
Given this concern, boronic acid **4** was subsequently protected by treatment with benzopinacol in refluxing THF/toluene using a Dean–Stark apparatus (Scheme 1).¹⁴ Benzopinacolate **1b** proved to be considerably more robust than the corresponding pinacolate **1a** and afforded the biotin–boronate ester **2b** cleanly and in good yield after coupling with **5** (Scheme 2) and with considerably less protodeboronated material.¹⁵

The precursor carboxylic acid **1b** and the biotin–boronate ester conjugate **2b** were tested as captors for aqueous [^{18}F]-fluoride via the formation of [^{18}F]-labeled aryltrifluoroborate PET imaging agents as described in the earlier report.³ Briefly, [^{18}F]-labeled trifluoroborates were synthesized by incubating $5\ \mu\text{L}$ of a $200\ \text{mM}$ Boronic acid/ester solution in DMF with $5\ \mu\text{L}$ $400\ \text{mM}$ KHF_2 solution pH 3–4 (4 equiv of fluoride), containing a minimum of $\sim 20\ \mu\text{Ci}$ of [^{18}F]-fluoride (radioactivity at the start of reaction).

After 1 h of labeling at room temperature, a $1\ \mu\text{L}$ aliquot of the labeling reaction was diluted 200-fold into $200\ \mu\text{L}$ of a solution of $200\ \text{mM}$ phosphate buffer pH 7.4 and $100\ \text{mM}$ [^{19}F]-KF and allowed to solvolyze for a



Scheme 1. Reagents and conditions: (a) *sec*-BuLi, TMEDA, THF, -78°C then $\text{B}(\text{OMe})_3$ then HCl, 75%; (b) R = Me, pinacol, THF/PhMe, 40°C , quant.; (c) R = Ph, benzopinacol, THF/PhMe, reflux, 72%.



Scheme 2. Reagents: (a) TFA, CH_2Cl_2 ; (b) **3** or **4**, EDC, HOBt, Base, CH_2Cl_2 .

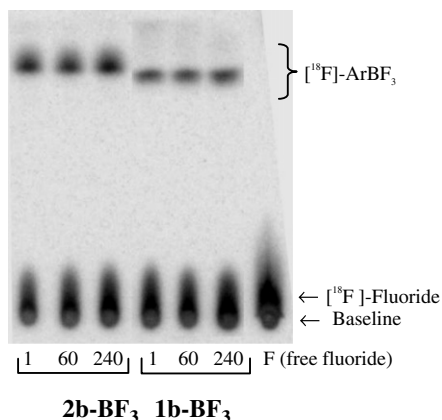


Fig. 1. Compounds **1b** and **2b** are converted to aryltrifluoroborates in the presence of [^{18}F]-fluoride in buffered KHF_2 pH 4.5. Following one hour of labeling, the fluoridation reaction is diluted 200-fold into 100 mM K^{19}F pH 7.5 for various time periods 1, 60, or 240 min. The aryltrifluoroborate is resolved from free fluoride using 5:95 $\text{NH}_4\text{OH}/\text{EtOH}$ and the TLC plate is subjected to autoradiography on a phosphor-storage screen. The relative autoradiographic density corresponding to the ArBF_3 and anionic fluoride can be quantified using the program IMAGEQUANT.

period of 240 min, 60 min, or 1 min. At the end point, a volume of 0.5 μL from each 'chase reaction' was spotted on a TLC plate and resolved in 5:95 $\text{NH}_4\text{OH}/\text{EtOH}$. The ArBF_3 cleanly separated from free fluoride with an R_f of 0.9, as shown in Figure 1.

Any solvolytic loss of fluoride results in the corresponding difluoroborane, which under aqueous conditions would either hydrolyze completely to the boronic acid, or revert to the unlabeled [^{19}F]-containing aryltrifluoroborate isotopolog. Furthermore, the large excess of [^{19}F]-KF added after labeling prevented any recapture of [^{18}F]-fluoride by a fully hydrolyzed boronic acid upon drying of the TLC plate dried.

Because thermodynamics dictate that at equilibrium the [^{18}F]-fluorine atom from the aryltrifluoroborate must com-

pletely exchange (>99%) in the presence of the large excess of [^{19}F]-KF, this isotopic exchange experiment followed by TLC separation and autoradiography effectively enables us to gauge a time-dependent increase in free fluoride and a concomitant decrease in the trifluoroborate.^{2,3} Using IMAGEQUANTTM following autoradiography, the extent of isotopic exchange could be calculated using the method of initial rates or via a first-order decay fit shown in Figure 2 where the rate constants for solvolysis for the trifluoroborates of **1b** and **2b** are $1.6 \pm 0.4 \times 10^{-4} \text{ min}^{-1}$ and $2.8 \pm 0.9 \times 10^{-4} \text{ min}^{-1}$, respectively.

In this case, the trifluoroborates formed from compounds **1b** and **2b**, displayed very little fluoride exchange, following a 4-h incubation and TLC resolution.

The aqueous stability of **1b-BF₃** in phosphate buffer was also measured by ^{19}F NMR.^{3b} This method allows one to quantitate the hydrolysis of an aryltrifluoroborate by measuring the rate of decrease of the trifluoroborate signal and the rate of increase in free fluoride over a sufficiently long time period compared to the half-life of ^{18}F . No other mono- or difluorinated intermediates were observed, thus allowing the total solvolysis of the ArBF_3 to be governed by dissociation of the first fluoride in a single rate-limiting step that is best approximated by a pseudo first-order rate constant. The kinetics of solvolysis for 10 mM **1b-BF₃** in 100 mM phosphate buffer pH 7.5 were thus measured at 5 min, 1 h, 4 h, 9 h, and 24 h, where the integration values for ArBF_3 (~56 ppm) and free fluoride (~43 ppm) were fit to the equation $([\text{ArBF}_3]/([\text{ArBF}_3] + [\text{F}]))_t = ([\text{ArBF}_3] + [\text{F}])_0 e^{-k_{\text{obs}} t}$ and a rate constant of $6.8 \pm 0.4 \times 10^{-4} \text{ min}^{-1}$ was obtained (data not shown) and is in generally good agreement with the value obtained from the autoradiography. That the observed rate constant obtained from the autoradiographic analysis was a bit lower than obtained by ^{19}F NMR is due to the presence of 100 mM ^{19}F that reduces the k_{obs} value. The stability of 10 mM **1b-BF** in 200 mM phosphate buffer pH 5.7 was also measured to

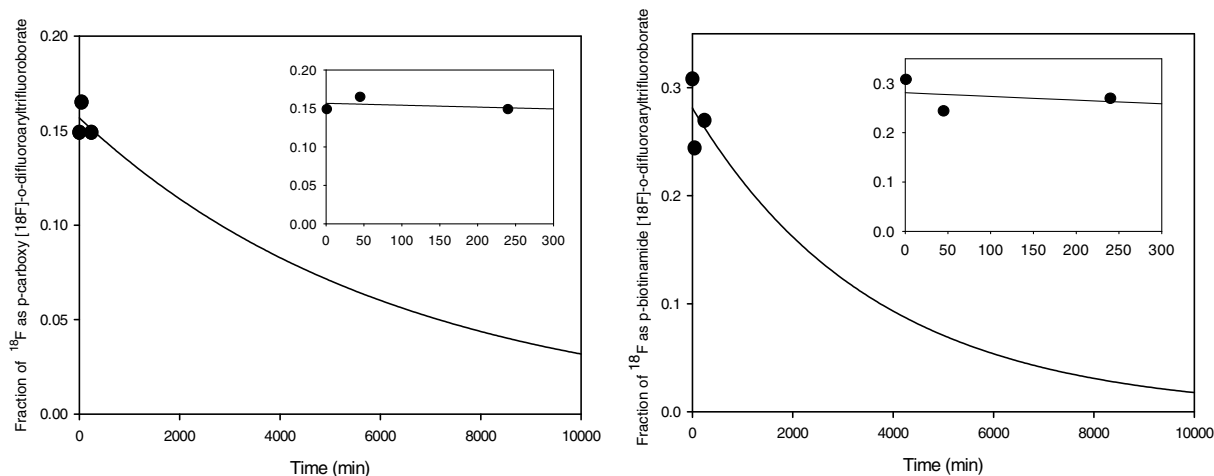


Fig. 2. Exponential decay fit for the trifluoroborates of compound A (left panel), and compound B (right panel), insets: relative amount of trifluoroborate over 240 min.

afford a rate constant of $3.5 \pm 1.5 \times 10^{-4} \text{ min}^{-1}$. This result demonstrates increased stability of **1b**–BF₃ at lower pH, conditions which reflect certain intracellular localizations should such an aryltrifluoroborate cross the cell membrane.

These data, taken together, indicate that this particular aryltrifluoroborate is kinetically very stable with respect to solvolytic defluoridation.

3. Conclusions

In summary, 2,6-difluoro-4-carboxyphenylboronic acid was readily prepared and easily protected as either its pinacol or the benzopinacol boronate ester. Further derivatization of both boronates with a biotinylated amine was accomplished smoothly under mild conditions to afford PET imaging precursors suitable for [¹⁸F]-labeling. This robust synthesis will allow for the attachment of **1** to other useful biomarkers besides biotin, examples of which will be reported in due course.

In order to demonstrate the kinetic stability of this aryltrifluoroborate with respect to solvolytic loss of fluoride, we used an isotopic exchange experiment that involved placing trace amounts of [¹⁸F]-trifluoroborate in a solution containing a large excess of [¹⁹F]-fluoride. This experiment measures the rate of loss of a single fluorine atom, as anionic fluoride, from the parent aryltrifluoroborate to afford the aryldifluoroborane, which is considered highly unstable in aqueous media. The resulting difluoroborane intermediate went undetected as it rapidly partitioned to either the fully hydrolyzed arylboronic acid/arylborate, or back to the aryltrifluoroborate, which is not radioactive as a consequence the large excess of [¹⁹F]-fluoride present.

Although it is uncertain whether the aryldifluoroborane completely hydrolyzed to the unlabeled arylboronic/arylborate or reacted with 100 mM aqueous [¹⁹F]-fluoride at pH 7.5 to regenerate the unlabeled aryltrifluoroborate isotopolog, nevertheless this experiment estimates the rate of loss of an atom of fluoride via a single rate-limiting step. Although only 3 time points were taken in this case leading to some error, it is clear that very little loss occurs over a period of 240 min, which is more than twice the half-life of the ¹⁸F-fluoride (see Ref. 3a). This aqueous stability was independently supported by a more thorough analysis using ¹⁹F NMR. Unless the presence of 100 mM free fluoride enhanced fluoride exchange, the same stability should be observed under physiological conditions (i.e., in vivo) and as such *this* trifluoroborate should be cleared from the blood stream to the bladder without solvolytic loss of [¹⁸F]-fluoride to the bone.

Acknowledgments

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5. Preparation of 2,6-difluoro-4-carboxyphenylboronic acid **2**: To a solution of 3,5-difluorobenzoic acid (1.20 g, 7.59 mmol) and TMEDA (2.50 mL, 16.7 mmol) in THF (50 mL) at -78°C was added a solution of *sec*-BuLi in cyclohexane (1.4 M, 13.0 mL, 18.2 mmol) and the reaction mixture was stirred at -78°C for 75 min. Neat trimethyl borate (1.80 mL, 16.1 mmol) was then added to the reaction at -78°C before warming the mixture to room temperature and stirring for 3 h. The reaction mixture was quenched with 3 N HCl (35 mL) and diluted with EtOAc (100 mL). The layers were separated and the organic layer was dried (Na₂SO₄) and concentrated. The resultant gray solid was washed thoroughly with hexanes (3 × 50 mL) and dried in vacuo to afford the title compound (1.15 g, 75%) as a white solid. All nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 or 400 MHz instrument. ¹H NMR spectra are referenced to the tetramethylsilane peak (δ 0.00), ¹⁹F NMR spectra are referenced to neat trifluoroacetic acid (δ 0.00, -78.3 ppm relative to CFCl₃) and ¹¹B NMR spectra are referenced to 15% BF₃·OEt₂ in CDCl₃ (0.00 ppm). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.45 (d, *J* = 7.4 Hz, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 165.6, 163.9 (dd, *J* = 243, 15 Hz), 134.6 (t, *J* = 9 Hz), 111.8 (d, *J* = 29 Hz), 111.8 (m); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -25.6 (d, *J* = 6.5 Hz, 2F); ¹¹B NMR (128 MHz, DMSO-*d*₆) δ 19.9; HRMS (ESI/MeOH) calcd for C₉H₈BO₄F₂[−] (M–H)[−] (dimethylboronate ester) 229.0484, found 229.0477.
6. Preparation of 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-bioxaborolan-2-yl)benzoic acid **3**: To a mixture of 2,6-difluoro-4-carboxyphenylboronic acid (114 mg, 0.56 mmol) and pinacol (66 mg, 0.56 mmol) were added THF (3 mL) and toluene (3 mL). The solvents were evaporated under reduced pressure at $\sim 40^\circ\text{C}$ to dryness. This procedure of solvent addition and evaporation was repeated two more times and the residue dried in vacuo to afford the title compound (159 mg, quant.) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.55 (d, *J* = 7.4 Hz, 2H), 1.40 (s, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 169.6, 166.2 (dd, *J* = 252, 12 Hz), 134.1 (t, *J* = 9 Hz), 112.7 (d, *J* = 29 Hz), 112.7 (m), 84.8, 24.7; ¹⁹F NMR (282 MHz, CDCl₃) δ -22.5 (d, *J* = 6.8 Hz, 2F); HRMS (ESI) calcd for C₁₃H₁₄BO₄F₂[−] (M–H)[−] 283.0953, found 283.0947.
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10. After shaking the DEAM-PS resin with **2** in freshly distilled THF for 1 h, the resin was filtered and rinsed with anhydrous THF (3 ×). The combined filtrates were concentrated and analyzed by ¹H and ¹⁹F NMR, indicating a $\sim 1:1$ mixture of **1:2**.

11. For selected examples of the use of *N*-methyldiethanolamine in the protection and isolation of arylboronic acids, see: (a) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717; (b) Abarca, B.; Ballesteros, R.; Blanco, F.; Bouillon, A.; Collot, V.; Dominguez, J.-R.; Lancelot, J.-C.; Rault, S. *Tetrahedron* **2004**, *60*, 4887–4893; (c) Yamamoto, Y.; Seko, T.; Nemoto, H. *J. Org. Chem.* **1989**, *54*, 4734–4736.
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13. Preparation of biotin–pinacolate **6**: A solution of *t*-butyl 5-biotinamidopentylcarbamate⁷ (15 mg, 0.035 mmol) in CH₂Cl₂/TFA (3:1, 1.3 mL) was stirred at room temperature for 3 h then concentrated in vacuo. The resultant oil was diluted with CH₂Cl₂ (2 × 5 mL) and toluene (1 × 5 mL) and concentrated in vacuo for 5 h. To a solution of the resultant TFA salt in anhydrous DMF (1.5 mL) were added pyridine (15 µL, 0.19 mmol), HOBt hydrate (6.8 mg, 0.050 mmol), 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-bioxaborolan-2-yl)benzoic acid **3** (12.6 mg, 0.044 mmol) and EDC (9.2 mg, 0.048 mmol) sequentially. The reaction mixture was stirred for 16 h then diluted with CHCl₃ (20 mL) and H₂O (5 mL). The aqueous layer was extracted with CHCl₃ (2 × 10 mL) and the combined organic extracts were dried (Na₂SO₄), concentrated, and washed with Et₂O (5 × 3 mL) to afford adduct **6** (12.5 mg, 60% over 2 steps) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.39 (d, *J* = 7.7 Hz, 2H), 7.13 (m, 1H), 5.97 (m, 1H), 5.84 (br s, 1H), 4.83 (br s, 1H), 4.51 (m, 1H), 4.33 (m, 1H), 3.46–3.11 (m, 6H), 2.92 (dd, *J* = 12.5, 4.4 Hz, 1H), 2.90 (br s, 1H), 2.73 (d, *J* = 12.8 Hz, 1H), 2.24–2.18 (m, 2H), 1.68–1.45 (m, 10H), 1.43 (s, 12H); ¹⁹F NMR (282 MHz, CDCl₃) δ –22.8 (d, *J* = 7.6 Hz, 2F); HRMS (ESI) calcd for C₂₈H₄₁BN₄O₅F₂SN⁺ (M+Na)⁺ 617.2756, found 617.2736.
14. Preparation of 2,6-difluoro-4-(4,4,5,5-tetraphenyl-1,3,2-bioxaborolan-2-yl)benzoic acid **4**: To a solution of 2,6-difluoro-4-carboxyphenylboronic acid (355 mg, 1.76 mmol) in toluene/THF (1:1, 30 mL) was added benzopinacol (709 mg, 1.93 mmol) and the mixture refluxed in a Dean–Stark apparatus for 16 h. The reaction mixture was cooled, concentrated, and purified by column chromatography on silica gel (CH₂Cl₂/MeOH; 98:2 then 95:5 then 90:10) to afford the title compound (0.67 g, 72%) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.71 (d, *J* = 6.7 Hz, 2H), 7.26–7.21 (m, 8H); 7.10–7.08 (m, 12 H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 166.7 (dd, *J* = 253, 12 Hz), 141.8, 134.9 (t, *J* = 9 Hz), 128.5, 127.3, 127.2, 113.0 (d, *J* = 29 Hz), 113.0 (m), 97.2; ¹⁹F NMR (282 MHz, CDCl₃) δ –21.0 (s, 2F); HRMS (ESI) calcd for C₃₃H₂₂BO₄F₂[–] (M–H)[–] 531.1579, found 531.1594.
15. Preparation of biotin–benzopinacolate **8**: A solution of *t*-butyl 5-biotinamidopentylcarbamate⁷ (15 mg, 0.035 mmol) in CH₂Cl₂/TFA (3:1, 1.3 mL) was stirred at room temperature for 3 h then concentrated in vacuo. The resultant oil was diluted with CH₂Cl₂ (2 × 5 mL) and toluene (1 × 5 mL) and concentrated in vacuo for 5 h. To a solution of the resultant TFA salt in anhydrous DMF (1.5 mL) were added pyridine (20 µL, 0.25 mmol), HOBt hydrate (7.5 mg, 0.056 mmol), 2,6-difluoro-4-(4,4,5,5-tetraphenyl-1,3,2-bioxaborolan-2-yl)benzoic acid **4** (25 mg, 0.047 mmol), and EDC (11.1 mg, 0.058 mmol) sequentially. The reaction mixture was stirred for 16 h then diluted with CHCl₃ (20 mL) and H₂O (5 mL). The aqueous layer was extracted with CHCl₃ (2 × 10 mL) and the combined organic extracts were dried (Na₂SO₄), concentrated, and purified by column chromatography on silica gel (CH₂Cl₂/MeOH; 96:4 then 90:10 then 85:15) to afford the boronate ester **8** (24 mg, 79% over 2 steps) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.51 (d, *J* = 7.8 Hz, 2H), 7.37 (m, 1H), 7.25–7.20 (m, 8H), 7.09–7.06 (m, 12H), 6.45 (m, 1H), 6.19 (br s, 1H), 5.25 (br s, 1H), 4.36 (m, 1H), 4.22 (m, 1H), 3.48–3.41 (m, 2H), 3.25–3.21 (m, 2H), 3.04–3.01 (m, 1H), 2.78 (dd, *J* = 12.5, 4.6 Hz, 1H), 2.64 (d, *J* = 13.0 Hz, 1H), 2.22–2.16 (m, 2H), 1.63–1.36 (m, 12H); ¹⁹F NMR (282 MHz, CDCl₃) δ –21.2 (d, *J* = 7.3 Hz, 2F); HRMS (ESI) calcd for C₄₈H₄₉BN₄O₅F₂SN⁺ (M+Na)⁺ 865.3382, found 865.3374.