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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

Andrew N. Cammidge* and Karen V. L. Crépy

Wolfson Materials and Catalysis Centre, School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich NR4 7TJ, United Kingdom

a.cammidge@uea.ac.uk

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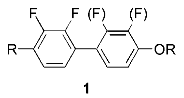
Abstract: A heavily functionalized atropisomeric biphenyl derivative (**4**), which is designed to possess a large lateral dipole moment, has been synthesized with use of a Suzuki coupling as the key step and resolved by chiral HPLC. The final coupling reaction is complicated by rapid hydrolytic deboronation 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 products[1] but is most commonly exploited in the field of asymmetric synthesis[2] 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]).



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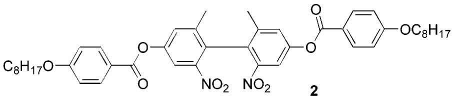

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With the above criteria in mind it is clear that atropisomeric biphenyls could fulfill the role of ideal dopants for smectic liquid crystals leading to chiral smectic C phases. Indeed the first examples of such materials have been reported recently 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 reaction[7] 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 reported[10] the first examples of intermolecular asymmetric Suzuki reactions[11] 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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(9) Fu has recently reported that Negishi coupling can be successfully employed to couple hindered substrates but noted that homocoupling was a significant side reaction when tetra-*o*-substituted biphenyls were synthesized: Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719.

(10) Cammidge, A. N.; Crépy, K. V. L. *Chem. Commun.* **2000**, 1723.

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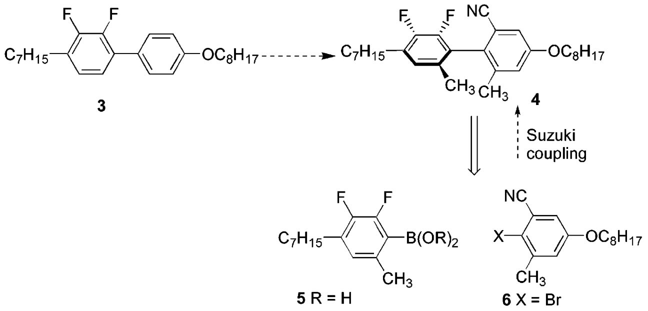
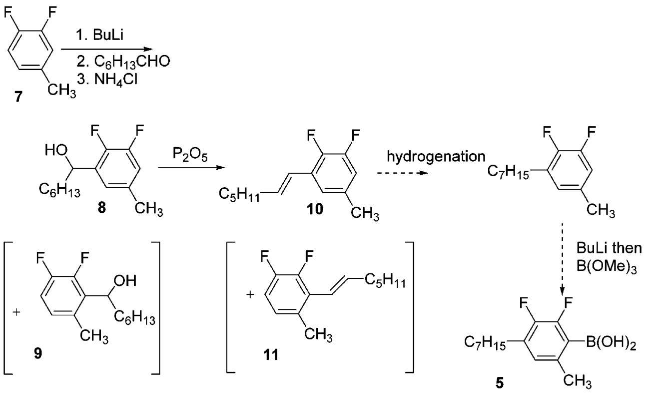
10.1021/jo034652s CCC: $25.00

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 values[13] 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 °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) iodide[14] 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/THF[15] 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 conditions[17] 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 acid[18] 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 peroxide[20] or sodium hypochlorite[21] 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 sieves[22] 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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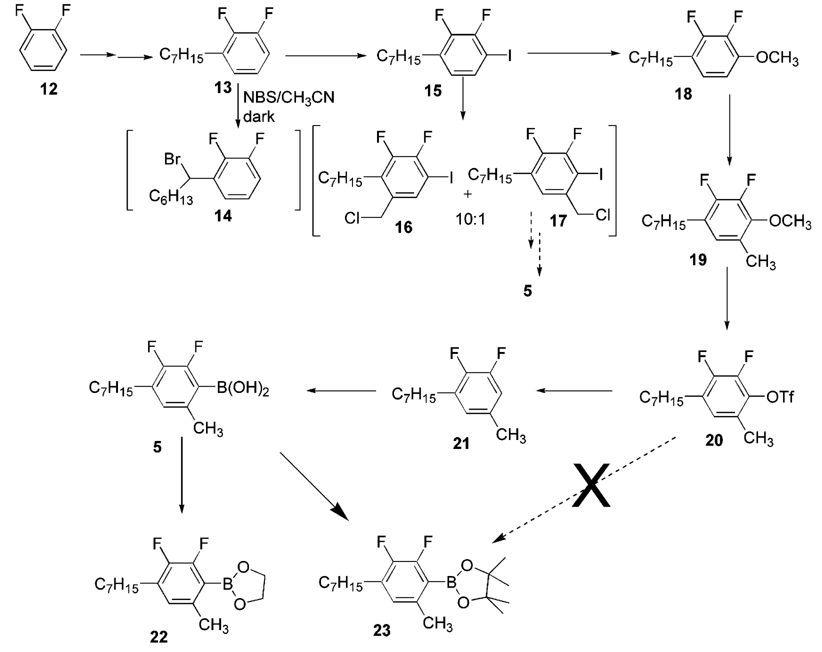
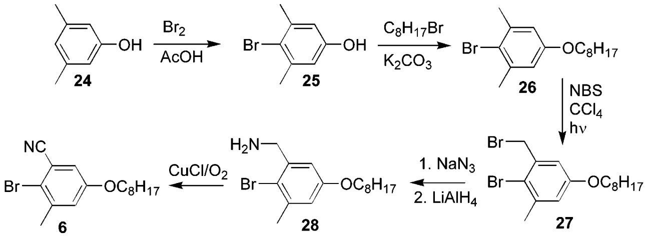
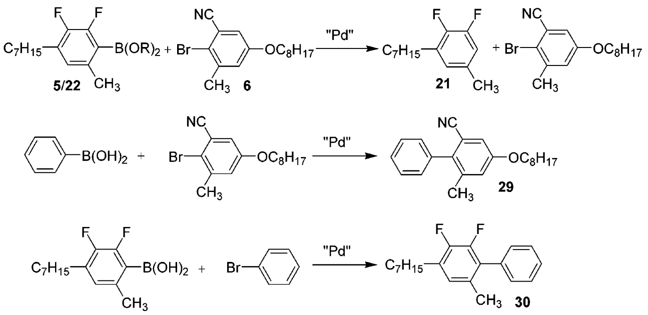
SCHEME 3. Synthesis of Boronic Acid 5 and Corresponding Boronate Esters



SCHEME 4. Synthesis of 6



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



preformed Pd(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 acids[23] 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 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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[23] Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett.* **1992**, 207.

[24] (a) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933. (b) Widdowson, D. A.; Zhang, Y.-Z. *Tetrahedron* **1986**, *42*, 2111.

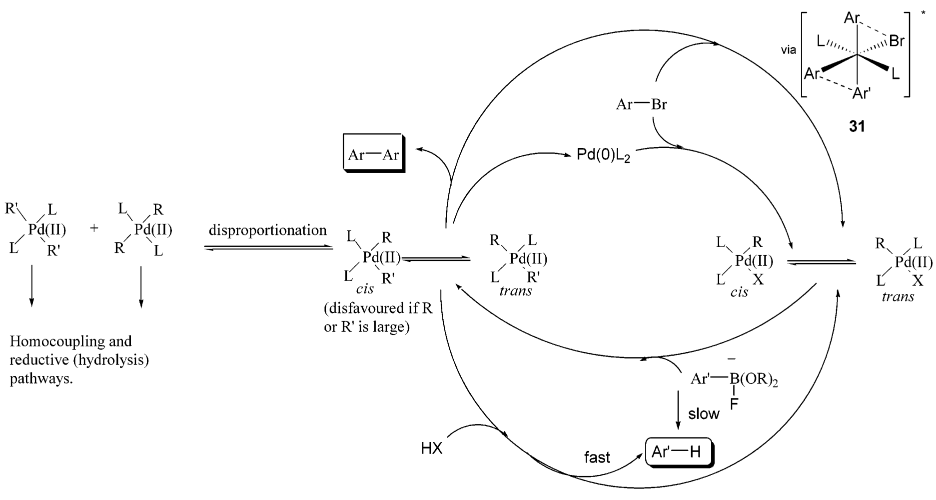


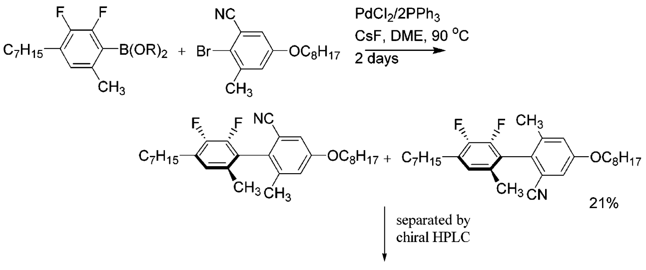
FIGURE 1. Catalytic cycle and side reactions.

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 $PdCl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$), ligand (such as PPh_3, dppf, dppe, $P(OMe)_3$), 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 $PdCl_2$ (3%)/PPh_3 (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.

SCHEME 6



Acknowledgment. We thank the EPSRC mass spectrometry service center at Swansea, UK for mass spectra and Takeda Chemical Industries Ltd for performing preparative chiral HPLC.

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.