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Synthesis of Enantiomerically Enriched Triarylmethanes by Enantiospecific Suzuki–Miyaura Cross-Coupling Reactions

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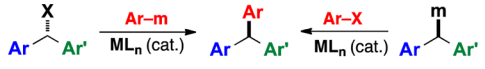
Supporting Information

ABSTRACT: The Suzuki–Miyaura cross-coupling of chiral, enantiomerically enriched dibenzylic boronic esters is described. The reaction proceeds with almost complete retention of stereochemistry, providing access to triarylmethanes, compounds that have high biological activity and are difficult to prepare in enantiomerically pure form using other methods.

The use of cross-coupling reactions to generate carbon–carbon bonds with stereochemistry has the potential to become an important tool for the construction of chiral molecules.[1] This technique permits the construction of C–C bonds in a traceless manner,[2] and therefore has the potential to be exceptionally valuable for the preparation of chiral hydrocarbons. Triarylmethanes are an important class of chiral hydrocarbons that have high biological activities and important materials properties.[3] Although there are a variety of racemic routes,[4] there are surprisingly few *enantioselective* or *enantiospecific* routes to this important class of chiral molecule.

We imagined that cross-coupling technology could provide a potentially valuable method for the synthesis of chiral triarylmethanes. However, the fact that enantioselective/enantiospecific cross-coupling chemistry is in its infancy compared to other Suzuki–Miyaura reactions increases the difficulty of accomplishing this goal.[5] Two complementary stereospecific cross-coupling approaches to triarylmethanes can be envisioned, as shown in Scheme 1. Starting from a chiral electrophile, a stereospecific coupling with an aryl metal reagent would provide the desired product with control of chirality (Scheme 1, left).

Scheme 1. Enantiospecific Coupling Approaches to Triarylmethanes

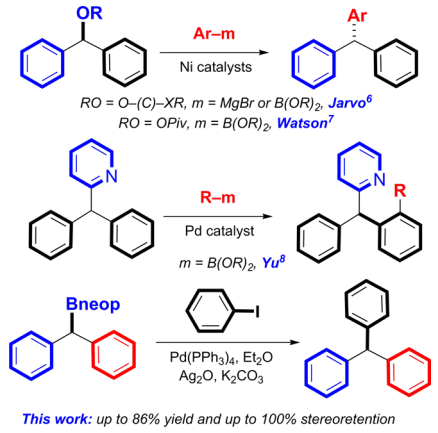


m = main group organometallic, **M** = transition metal, **X** = halide or pseudo halide

Alternatively, enantiomerically enriched nucleophiles, such as boronic esters, have the potential to serve as key chiral components in a stereospecific coupling approach to triarylmethanes (Scheme 1, right).

Recently, in seminal papers, Jarvo[6] and Watson[7] have shown that chiral dibenzylic ethers and esters are effective electrophiles in asymmetric routes to triarylmethanes (Scheme 2). Although

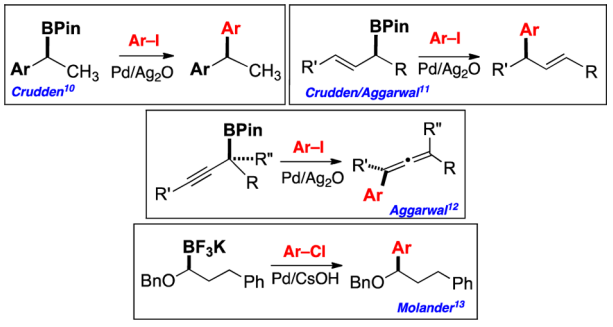
Scheme 2. Enantioselective/Enantiospecific Routes to Unsymmetrical Triarylmethanes



innovative C–H activation[8] and Friedel–Crafts methods[9] preceded these publications, the coupling approaches reported by Jarvo and Watson provide triarylmethanes with fewer substrate restrictions.

One important class of molecules that performs well in the enantiospecific Suzuki–Miyaura cross-coupling is composed of molecules with π-unsaturation adjacent to the C–B bond of interest. Thus, our group has demonstrated that chiral, enantiomerically enriched benzylic[10] and allylic[11] boronic esters undergo largely or completely stereospecific coupling, and Aggarwal[12] and Molander[13] have described similar results with related chiral nucleophiles (Scheme 3).[14] Thus, we set out to

Scheme 3. π-Directed Stereospecific Cross-Couplings



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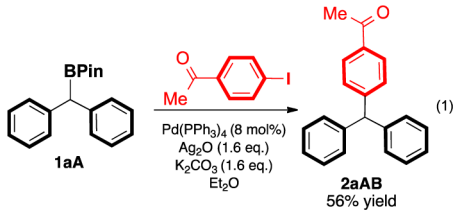
determine whether enantioenriched boronic ester nucleophiles would be effective coupling partners for the synthesis of enantiomerically enriched triarylmethanes via cross-coupling chemistry. As described herein, the proposed coupling reaction can be effected under straightforward conditions with up to 100% enantioretention.

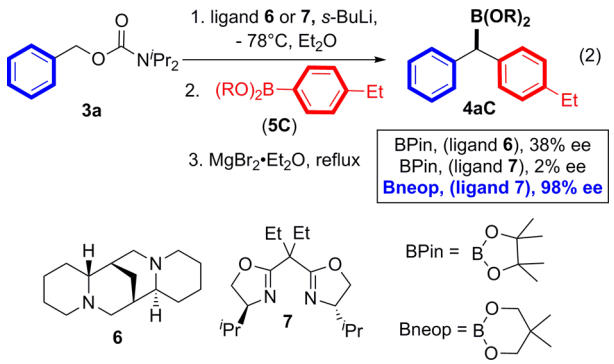
As a preliminary test of feasibility, we employed $Pd(PPh_3)_4$ and Ag_2O for the reaction of dibenzylic boronic ester **1aA** with *p*-iodoacetophenone. To our delight, the desired product was obtained in reasonable yield without significant optimization (eq 1). Compared to the conditions previously reported for the



coupling of monobenzylic[10,15] or allylic[11] boronic esters by our group, some slight but important differences should be noted. Diethyl ether proved to be a significantly better solvent than any other examined, and, as in the cross-coupling of allylic systems, high loadings of PPh_3 were not required. In fact, optimal conditions require only $Pd(PPh_3)_4$ with no added phosphine.

In order to develop this route into a synthesis of *enantioenriched* triarylmethanes, the enantioselective synthesis of the starting dibenzylic boronic esters was required. To this end, we initially examined Matteson chemistry for the preparation of chiral versions of **1**,[16] but found that the intermediate benzylic chloroboronic ester was too unstable. Aggarwal chemistry[17] was next attempted in an effort to generate the desired boronic ester in high enantiomeric purity. Although this chemistry has been widely used for the synthesis of a range of compounds with high enantiomeric purity, the use of a *benzylic* carbamate such as **3**, which was required for our method, was unprecedented.

Thus, we proceeded to examine the suitability of benzylic carbamate **3a** in the enantioselective synthesis of target organoborane **4aC**. In the event, treatment of **3a** with *s*-BuLi and (−)-sparteine (**6**), followed by 2-(4-ethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5C**), at low temperature gave the desired four-coordinate borate ester, which was induced to rearrange by treatment with freshly generated $MgBr_2$ upon warming to reflux (eq 2). Although this method generated the

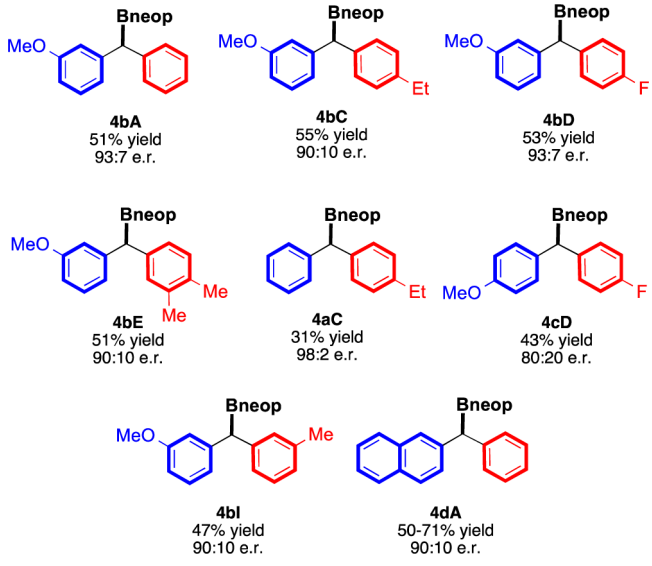


desired product, the levels of enantioselectivity were too low to be of synthetic utility, a consequence of the significant competition between the desired displacement of the carbamate via 1,2-migration of the organoborate, and the back reaction regenerating the stable benzylic organolithium species. Generating this species at temperatures above −30 °C leads to racemization.[18]

Benzylic carbamates have, however, been reported to participate successfully in enantioselective lithiation chemistry under different conditions. For example, Hoppe has reported the use of bisoxazolines as ligands for the generation of benzylic organolithium species directly derived from **3a**, followed by the highly enantioselective trapping of a variety of small electrophiles, including CO_2.[19] Unfortunately, the bisoxazoline **7** used by Hoppe gave even lower enantioselectivity when applied to the borylation of lithiated **3a**. Consistent with Aggarwal's report that the bulk of the substituents on boron can have a negative effect on stereocontrol in related 1,2-metalate rearrangements,[12] we found that 2,2-dimethylpropanediol-derived boronic esters (Bneop) were significantly superior to related pinacol derivatives, resulting in a remarkably improved synthesis of the desired dibenzylic boronic ester **4aC**.[20] These conditions provided dibenzylic boronic ester **4aC** with unprecedented enantioselectivity (eq 2).

Unsurprisingly, the reaction proved sensitive to the electronics of the arene bound to the carbamate. However, arenes that are electronically neutral, or those in which functionality is not directly correlated to the benzylic carbon (i.e., through the *para* position), provided the desired boronic esters in good to high enantioselectivities (Chart 1). The only

Chart 1. Enantiomerically Enriched Dibenzylic Boronic Esters



drawback to this method is the increased sensitivity of the neopentyl boronic esters to chromatography, which manifests itself in reduced isolated yields for these compounds on small scale. However, the reaction proceeded in good yield (73% for **4dA**, Chart 2) when performed on gram scale. The enantioselective equivalent was performed reliably on 0.5 g scale. The use of good quality *s*-BuLi is critical for this step.

With a method for the synthesis of enantioenriched dibenzylic boronic esters in hand, the next step was to engage these compounds in cross-coupling reactions with the aim of synthesizing enantiomerically enriched triarylmethanes. Gratify-

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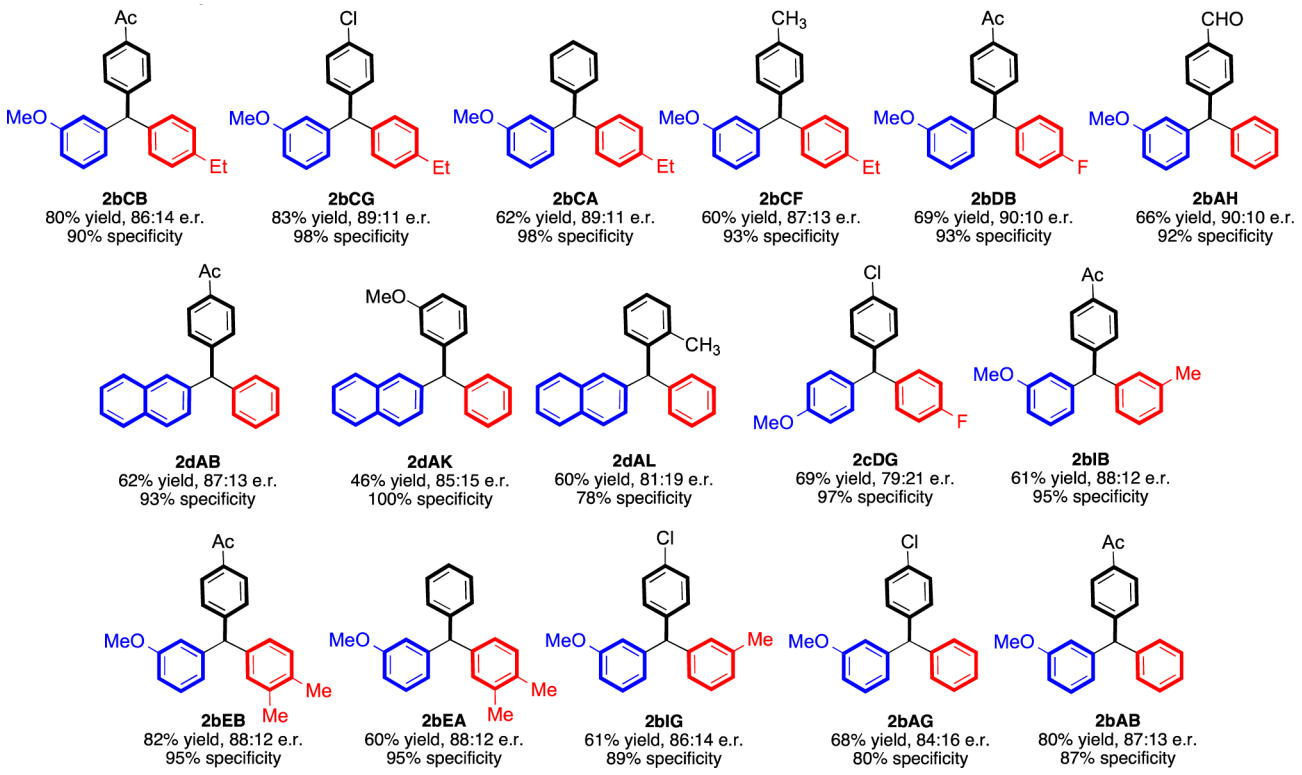
Chart 2. Enantiomerically Enriched Triarylmethanes Prepared via Cross-Coupling of Boronic Esters from Chart 1



ingly, the cross-coupling reactions proceeded with a variety of aryl iodides to give the desired enantiomerically enriched triarylmethanes with enantiospecificities typically in the high 90s[21] (Chart 2). Yield and specificity had little correlation with the electronics of the aryl iodide, such that chloro-, acetyl-, and formyl-substituted aryl iodides reacted similarly as electron neutral aryl iodides. The reaction was somewhat sensitive to sterics, with a noticeably lower enantiospecificity observed with *o*-iodotoluene (compare **2dAL** with **2dAB** and **2dAK**, Chart 2). Although heteroatom-substituted partners were not exhaustively studied, 3-iodopyridine reacted, but at higher temperatures (85 °C) leading to considerable racemization (see Supporting Information).

Having developed a viable Suzuki–Miyaura cross-coupling approach for the synthesis of triarylmethanes, we then examined whether the reaction proceeded with retention or inversion of stereochemistry. Previous reports from our group[10,11b] and those of Molander[13] and Aggarwal[12] show that related couplings facilitated by unsaturation in the starting material (benzyl, allyl, propargyl, or benzyl ether) proceed with retention of configuration. In contrast, the heteroatom-directed coupling chemistry of chiral organoboranes developed by Suginome,[14a,b] Hall,[14c] and Molander[14d] proceeds with *inversion* of stereochemistry. Considering that the coupling of dibenzylic boronic esters reported herein is aided by two sites of (benzylic) unsaturation, retention of configuration was expected.

The dearth of synthetic methods for the production of enantiomerically enriched triarylmethanes complicated the determination of absolute stereochemistry. Thus, we turned to crystallography and prepared the bromophenyl hydrazone of coupling product **2bAH** that possesses an aldehyde functionality (Figure 1). When the absolute configuration, as determined by X-ray analysis, was compared with the optical

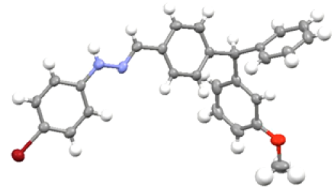


Figure 1. X-ray crystallographic analysis of hydrazone **8bAH** showing *R* stereochemistry. Thermal ellipsoids are shown at 50% probability.

rotation of the alcohol derived from benzylic boronic ester **4bA**, it was determined that the coupling reaction proceeded with retention of configuration (see Supporting Information).

In addition, since the absolute configuration of the alcohol derived from **4dA** and the product of the coupling of **4dA** with 4-iodoacetophenone (**2dAB**) were both known in the literature,[6b] comparison of the optical rotations obtained in our study was also consistent with retention of stereochemistry during the coupling reaction.[10−13,15]

In conclusion, we have demonstrated that the Pd-catalyzed Suzuki–Miyaura coupling of enantioenriched dibenzylic boronic esters can be carried out with good to excellent stereoretention, representing one of only a few methods available for the enantioselective synthesis of triarylmethanes. In addition, this work describes the first enantioselective synthesis of dibenzylic boronic esters and contributes to the small but expanding number of stereospecific cross-coupling techniques in the literature.

■ ASSOCIATED CONTENT

Supporting Information

Spectral data, experimental procedures, X-ray crystallographic data, and detailed information on the assignment of stereo-

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chemistry. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(21) es = (%ee product/%ee starting material) × 100%