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Enantiospecific Synthesis of ortho-Substituted 1,1-Diarylalkanes by a 1,2-Metalate Rearrangement/anti-S_N2' Elimination/Rearomatizing Allylic Suzuki–Miyaura Reaction Sequence

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Abstract: The one-pot sequential coupling of benzylamines, boronic esters, and aryl iodides has been investigated. In the presence of an N-activator, the boronate complex formed from an ortho-lithiated benzylamine and a boronic ester undergoes stereospecific 1,2-metalate rearrangement/anti-S_N2' elimination to form a dearomatized tertiary boronic ester. Treatment with an aryl iodide under palladium catalysis leads to rearomatizing γ-selective allylic Suzuki–Miyaura cross-coupling to generate 1,1-diarylalkanes. When enantioenriched α-substituted benzylamines are employed, the corresponding 1,1-diarylalkanes are formed with high stereospecificity.

The 1,1-diarylalkane motif is found in many biologically relevant molecules and, as a result, approaches to its stereocontrolled synthesis have garnered considerable attention in recent years. A remarkably diverse array of reactivity platforms has been developed for its synthesis, including the decarbonylation of β,β-diarylpropionaldehydes, the hydrogenation of 1,1-diarylalkanes, and the difunctionalization of both alkyl- and aryl-substituted alkenes. A more convergent strategy is the Ni-catalyzed cross-coupling of benzylic electrophiles, through both enantiospecific and enantioconvergent pathways. Alternatively, benzylic nucleophiles, such as boron reagents, can be used. For example, Crudden has described the stereospecific Pd-catalyzed cross-coupling of benzylic electrophiles, through both enantiospecific and enantioconvergent pathways. However, when many methods are restricted to naphthyl-based or sterically unencumbered substrates.

We recently reported a method for the enantiospecific synthesis of ortho-substituted secondary benzylic boronic esters. Enantioenriched α-methyl o-bromo benzylamines were transformed into dearmatized intermediate 4 through a 1,2-metalate rearrangement/anti-S_N2' elimination reaction triggered by N-activation of arylboronate complex 2' (Scheme 1B). Subsequent suprafacial 1,3-borotropic shift provided the secondary α-methyl benzylic boronic esters (5) with excellent levels of enantiopurity. We recognized that the stereospecific cross-coupling of these enantioenriched benzylic boronic esters with an aryl electrophile, in line with reports from Crudden, would provide access to the valuable 1,1-diarylalkane motif. A more direct route to such motifs, however, would be through the interruption of the cascade sequence at the dearmatized intermediate 4, engaging this species in a rearomatizing γ-selective allylic Suzuki–Miyaura cross-coupling (Scheme 1C). We envisioned that such a pathway, passing through a six-membered ring transition state, TS-I, would allow transfer of the chiral information in 4 and provide a route to enantioenriched 1,1-diarylalkanes with extensive functionalization in the ortho position. Herein, we report the realization of this process, which proceeds through two consecutive stereospecific 1,3-transpositions of stereogenicity, including a 1,2-metalate rearrangement/anti-S_N2'.

Scheme 1. Access to 1,1-diarylalkanes.

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elimination and a syn-S_N2′-γ-selective Suzuki–Miyaura reaction, to provide a one-pot procedure to transform enantioenriched α-branched benzyamines into enantioenriched 1,1-diarylalkanes bearing considerable steric congestion in the ortho position.

We began our studies with dearomatized tertiary boronic ester 4aa, which was chosen because it can be isolated by column chromatography (see Supporting Information for details) and can be accessed through our previously reported 1,2-metalate rearrangement/anti-S_N2′-elimination reaction. After optimization (see Supporting Information for details), cross-coupled product 6aaa was formed in 98% 1H NMR yield (Scheme 2A). We then undertook optimization of the one-pot procedure. Dearomatized tertiary boronic ester 4aa was generated by successive treatment of ortho-bromo naphthylamine 1a with nBuLi, to form ortho-lithiated naphthylamine; cyclohexylboronic acid pinacol ester (CyBpin, 2a), giving the arylboronate complex; and the N-activator, Me₂Troc-Cl, to promote 1,2-metalate rearrangement/anti-S_N2′-elimination. The reaction mixture was then treated with Ag₂O, followed by Pd(dbac), RuPhos, and iodosobenzene (3a) and heated to 75°C for 6 h. While some of the desired product 6aaa was observed, the yield was considerably lower (8%) than that obtained when using isolated 4aa. Pleasingly, changing the silver salt from Ag₂O to Ag₂CO₃ and optimizing the stoichiometry led to a significant improvement in yield (90%). Furthermore, reducing the temperature from 75°C to 50°C had no detrimental effect on the yield, providing 6aaa in 92% yield as determined by 1H NMR (Scheme 2B). Interestingly, the 1H NMR spectrum of the purified material contained two sets of signals in a ratio of 87:13, which were shown to interconvert through variable temperature 1H NMR experiments. We identified a coalescence temperature of 55°C and determined a rate of exchange from the minor to the major species was 18 h with improved yields, providing coupled product 6aah in 92% yield. Phenylboronic ester 2b also underwent coupling to provide biaryl 6aha in 76% yield. In line with previous reports, the 1,2-boron-to-carbon migration proceeded with excellent levels of retentive enantiospecificity, providing chiral products in high e.r. (6aia, 95:5 and 6bai, 98:2) and d.r. (6baa, >95:5 and 6aba, >95:5). These substrates also highlight the functional group tolerance of the process, with tert-butyl carboxyesters, azides, and TBDPS-protected alcohols tolerated.

We then assessed the scope of the aryl iodide and benzyamine coupling partners (Table 1, parts B and C). The electronics of the aryl iodide appeared to have limited effect on reactivity and both electron-donating (6aab) and electron-withdrawing substituents (6aac) were well tolerated, as were halides (6aad, 6aee, 6aaf) and ortho-substitution (6aag). Nitrogen heterocycles could also be incorporated, giving coupled product 6aah, albeit in reduced yield. Simple ortho-bromo benzylamine 1b underwent smooth coupling to provide 6baa in 67% yield. Electron-rich and electron-poor benzyamines were viable substrates, providing 6caaa and products 6dai–6gai. Ortho-substitution was tolerated, as illustrated by bis-ortho-substituted product 6dai, and heteroaryl benzyamines could also be used, as highlighted by benzo[bicyclo[2.2.1]hept-5-en-2-yl]amine 1h, which provided product 6hai in moderate yield.

We then turned our attention towards the synthesis of enantioenriched 1,1-dimethyl-1,1,1-trichloro-1,1-dimethyl ethyl chloroformate.

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yield and 91:9 e.r., corresponding to an enantiospecificity of 84% from (R)-1 i.

Since 4i a is formed in 96:4 e.r., this result indicates that the g-selective allylic Suzuki–Miyaura cross-coupling (4i a to 6 iaa) proceeds in 87% es. For comparison, we prepared and tested a-methyl benzylic boronic ester 5i a (94:6 e.r.) under Crudden/C29s cross-coupling conditions, which provided 24% of 6 iaa in 88:12 e.r. (86% es), along with 30% b-hydride elimination product 7, 30% of returned starting boronic ester 5i a and 4% protodeboronation product 8 (Scheme 3B). The lower yield and formation of side-products is a consequence of the considerable steric hindrance of boronic ester substrate 5i a, highlighting a positive feature of the new process which does not suffer from the same issues.

To further highlight the utility of this methodology, doubly stereospecific transformations were carried out using both enantiomers of a-methyl benzylamine 1i and (S)-menthol-derived boronic ester 2m (Scheme 3 C). Coupling with (R)-1 i provided product 6ima in 40% isolated yield and > 95.5 d.r. and the enantiomeric a-methyl benzylamine (S)-1 i gave the diastereomeric product 6ima' in 44%, again in excellent d.r. (> 95.5). Additionally, reaction of enantioreriched boronic ester 2n with (R)-1 i and (S)-1 i afforded diastereomeric products 6ima and 6ima', respectively, both with > 95.5 d.r. (Scheme 3C). These examples indicate that no matched/ mismatched effects occur between the benzylamine and boronic ester components.

Table 1: Substrate scope.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield (e.r.)</th>
<th>Diastereomeric Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>6aa a</td>
<td>85%</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>6ab a</td>
<td>94%</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>6ac a</td>
<td>85%</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>6ac b</td>
<td>83%</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>6aa c</td>
<td>84%</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>6afa</td>
<td>60%</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>6aga</td>
<td>88%</td>
<td>&gt; 95:5</td>
</tr>
</tbody>
</table>

[a] Reactions were performed using 0.3 mmol of 3, 1.5 equiv of 1, 2, nBuLi (1.6 m in hexanes) and Me3Troc-Cl, 3 equiv of Ag2CO3, 5 mol % of Pd(dba)2, and 10 mol % of RuPhos. See Supporting Information for exact experimental procedures. Yields refer to isolated products unless otherwise indicated. Diastereomeric ratios were determined by 1H NMR analysis of the purified compounds. [b] Final cross-coupling step at RT for 18 h. [c] Yield determined by 1H NMR analysis of the crude reaction mixture using dibromomethane as internal standard. [d] Cross-coupling step at 75°C for 5 h.
through four sequential processes into the final coupled product with high stereospecificity.

In conclusion, we report a new method for the synthesis of enantioenriched 1,1-diarylethane derivatives. Through a series of four stereospecific steps, enantioenriched α-methyl benzylamines are transformed into valuable optically active 1,1-diarylethanes with good stereospecificity. In terms of reactivity, the key syn γ-selective allylic Suzuki–Miyaura cross-coupling process appears to overcome structural limitations encountered in the traditional direct cross-coupling of certain sterically hindered secondary benzylic boronic esters. The highly convergent nature of this coupling process affords sterically encumbered 1,1-diarylethanes with three readily addressable points of diversification.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,1-diarylethane · boronic ester · cross-coupling · one-pot · stereospecific

[1] For examples of 1,1-diarylekanes with biological activity, see:

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Communications


The stereochemistry of 6ima was confirmed by X-ray crystallography.

Subjecting primary benzyllic boronic ester 5ba to these conditions does, however, provide coupled product 6baaa in 21% NMR yield, along with 21% recovered 5ba (see Supporting Information for details). Thus, for benzylamines without substituion (for example, 1b), we cannot rule out a minor pathway that proceeds through 1,3-borotrophic shift followed by direct Suzuki–Miyaura cross-coupling.

Iodo-3-methoxybenzene (3) was used in place of iodobenzene (3a) in some examples if it facilitated purification, particularly from homocoupling product.

The enantiospecificity (es) was calculated as follows: es = [(% ee of starting material) × 100]

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