Rubial, B., Collins, B. S. L., Bigler, R., Aichhorn, S., Noble, A., & Aggarwal, V. K. (2019). Enantiospecific Synthesis of ortho-Substituted 1,1-Diarylalkanes by a 1,2-Metalate Rearrangement/anti-SN2 Elimination/Rearomatizing Allylic Suzuki–Miyaura Reaction Sequence. Angewandte Chemie - International Edition, 58(5), 1366-1370. https://doi.org/10.1002/anie.201811343

Publisher's PDF, also known as Version of record

License (if available):
CC BY

Link to published version (if available):
10.1002/anie.201811343

Link to publication record in Explore Bristol Research
PDF-document

This is the final published version of the article (version of record). It first appeared online via Wiley at https://onlinelibrary.wiley.com/doi/full/10.1002/anie.201811343. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research
General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/pure/about/ebr-terms
Enantiospecific Synthesis of ortho-Substituted 1,1-Diarylalkanes by a 1,2-Metalate Rearrangement/anti-S_{N}2' Elimination/Rearomatizing Allylic Suzuki–Miyaura Reaction Sequence

Belén Rubial*, Beatrice S. L. Collins*, Raphael Bigler, Stefan Aichhorn, Adam Noble, and Varinder K. Aggarwal*

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_{N}2' 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.[1] A remarkably diverse array of reactivity platforms has been developed for its synthesis, including the decarbonylation of β,β-dialkylpropanaldehydes,[2] the hydrogenation of 1,1-diarylalkanes,[3] and the difunctionalization of both alkyl- and aryl-substituted alkenes.[4] A more convergent strategy is the Ni-catalyzed cross-coupling of benzylic electrophiles, through both enantiospecific[5] and enantioconvergent[6] pathways. Alternatively, benzylic nucleophiles, such as boron reagents, can be used. For example, Crudden has described the stereospecific Pd-catalyzed cross-coupling of benzyltriphenylphosphonium salts with secondary benzylic boronic esters.[7] We recently reported a method for the enantiospecific synthesis of ortho-substituted secondary benzylic boronic esters.[8] Enantioenriched α-methyl o-bromo benzylamines were transformed into dearomatized intermediate 4 through a 1,2-metalate rearrangement/anti-S_{N}2' elimination reaction triggered by N-activation of aryloborate complex 2' (Scheme 1B). Subsequent suprafacial 1,3-borotropic shift provided the secondary α-methyl benzylic boronic esters (5) with excellent levels of enantipurity. We recognized that the stereospecific cross-coupling of these enantioenriched benzylic boronic esters with an aryl electrophile, in line with reports from Crudden,[7] would provide access to the valuable 1,1-diarylalkane motif.[9] A more direct route to such motifs, however, would be through the interruption of the cascade sequence at the dearomatized intermediate 4, engaging this species in a rearomatizing γ-selective allylic Suzuki–Miyaura cross-coupling (Scheme 1C).[10] 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_{N}2'
elimination and a syn-S,S' γ-selective Suzuki–Miyaura reaction, to provide a one-pot procedure to transform enantioenriched α-branched benzylamines into enantioenriched 1,1-diaryalkanes 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-metallate rearrangement/anti-S,S' 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-metallate rearrangement/anti-S,S' elimination. The reaction mixture was then treated with Ag2O, followed by Pd(dbstruction); RuPhos, and iodobenzene (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 of 30.9 Hz (Scheme 2C). [13] Further 1H NMR experiments, these studies led us to assign the two sets of signals as rotamers, 6aaa-Ra and 6aaa-Rb, where interconversion occurs through rotation of the naphthyl-cyclohexyl C–C bond (Scheme 2C). [13] Furthermore, NOESY correlations support the assignment of the major rotamer as 6aaa-Ra. Having identified the two sets of signals as rotamers, we were then able to confirm that 6aaa was isolated in 88% yield. [14]

With the optimized conditions in hand, we went on to investigate the scope of the three-component coupling reaction (Table 1, part A). Symmetrical cyclic secondary boronic esters gave coupled products 6aaa–6ada in excellent isolated yields. While cyclohexyl product 6aaa showed rotamer behaviour by 1H NMR, cyclopentyl (6aba), cyclobutyl (6aca), and cyclopropyl (6ada) coupled products were observed as single species. An acyclic secondary boronic ester also coupled smoothly, providing 6aea in 84% yield, while broadening of the methylene signal indicated restricted rotation on the 1H NMR timescale. For primary alkylboronic esters, the reaction was performed at room temperature for 18 h with improved yields, providing coupled product 6afa in 66% yield. Interestingly, the homocoupling of the dearomatized intermediate could also be isolated in 8% yield. We attribute this product to an alternative mechanism, involving double transmetalation at a palladium(II) center, followed by reductive elimination and re-oxidation using Ag2CO3 as a terminal oxidant. No coupling product was observed with sterically demanding tertiary boronic ester 2g; use of benzylamine 1b, however, led to coupled product 6bga in excellent yield (885%). Phenyloboronic ester 2h also underwent coupling to provide biaryl 6bha 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. (6bha, 95:5 and 6bja, 98:2) and d.r. (6aka, >95:5 and 6ala, >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 benzylamine 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, 6aae, 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 benzylamines were viable substrates, providing 6caa and products 6dai–6gai. Ortho-substitution was tolerated, as illustrated by bis-ortho-substituted product 6dai, and heteroarylbenzylamines could also be used, as highlighted by benzothiophenyl amine 1h, which provided product 6hai in moderate yield. [13]

We then turned our attention towards the synthesis of enantioenriched 1,1-diarylethylene derivatives. α-Methyl benzylamine (R)-11 (99:1 e.r.) was subjected to the standard reaction conditions using cyclohexyloboronic ester 2a (Scheme 3 A). Coupled product 6fia was formed in 50% 1H NMR.
yield and 91:9 e.r., corresponding to an enantiospecificity of 84% from \((R)-1i\). 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 \(\alpha\)-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 \(\alpha\)-methyl benzylamine \(1i\) and \((-\) -menthol-derived boronic ester \(2m\) (Scheme 3 C). Coupling with \((R)-1i\) provided product \(6ima\) in 40% isolated yield and > 95:5 d.r. and the enantiomeric \(\alpha\)-methyl benzylamine \((S)-1i\) gave the diastereomeric product \(6ima'\) in 44%, again in excellent d.r. (> 95:5). Additionally, reaction of enantioenriched boronic ester \(2n\) with \((R)-1i\) and \((S)-1i\) afforded diastereomeric products \(6ina\) and \(6ina'\), respectively, both with > 95:5 d.r. (Scheme 3 C). These examples indicate that no matched/mismatched effects occur between the benzylamine and boronic ester components.

While secondary boronic ester \(5ia\) does undergo direct cross-coupling to provide cross-coupled product \(6ina\) when subjected to Crudden’s conditions (Scheme 3 B), we believe that a 1,3-borotropic shift/direct cross-coupling pathway for \(\alpha\)-methyl benzylamine \((R)-1i\) is unlikely. To rule out such a pathway, we subjected boronic ester \(5ia\) to our reaction conditions, and observed no evidence of cross-coupled product \(6ina\) (Scheme 4 A). Furthermore, naphthylamine \(1a\), which has been used extensively as a substrate in these studies, is stable with respect to the 1,3-borotropic shift: heating \(4a\) a in the presence of NaBPh 4, in line with our previously reported conditions, provided no evidence of the borotropic shift product (Scheme 4 B). Moreover, heating \(4aa\) in the presence of Ag 2CO3, in analogy to our optimized allylic cross-coupling conditions, also showed no reactivity towards 1,3-borotropic shift. We thus propose that the transformation of \(\alpha\)-methyl benzylamines into 1,1-diarylethane derivatives proceeds through a series of four highly stereospecific processes: 1) a stereospecific 1,2-metalate rearrangement that occurs concurrently with 2) a stereospecific \(anti-S\) elimination of the \(N\)-acylated leaving group to give the dearomatized intermediate, 4, followed by 3) a stereospecific \(syn\gamma\)-selective allylic transmetalation via a six-membered transition state to give intermediate 5 and 4) a stereospecific retentive reductive elimination (Scheme 4 C). In this way, the chirality in the starting \(\alpha\)-methyl benzylamine is transferred.

### Table 1: Substrate scope[^a]

| Substrate scope | 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.

Acknowledgements

We thank the EPSRC (EP/I038071/1), and H2020 ERC (670668) for financial support. B.R. thanks the Principality of Asturias and the EU for a Clarin-COFUND postdoctoral grant (ACA17-23). S.A. thanks the Austrian Science Fund (FWF) for an Erwin Schrödinger fellowship (J3919-N28). R.B. thanks the Swiss National Science Foundation fellowship program (P2EJP2 165268). We thank Dr. H. Sparkes for X-ray crystallography of 6ima', and Prof. C. Butts and Prof. J. Clayden for helpful discussions.

Conflict of interest

The authors declare no conflict of interest.

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

For examples of 1,1-diarylelanes with biological activity, see:

a) K.-L. Yu, P. Spinazzee, J. Ostrowski, S. J. Currier, E. J. Pack, L. Hammer, T. Roalsvig, J. A. Honeyman, D. R. Tortolani, P. R.
[5] For stereospecific Suzuki–Miyaura cross-couplings of benzylic organoboron compounds, see: a) B. L. H. Taylor, E. C. Swift, J. D. Waetzig, E. R. Jarvo, J. Am. Chem. Soc. 2009, 131, 12344; b) X. Wang, A. Guram, S. Caille, J. Hu, J. P. Preston, M. Ronk, S. Walker, Org. Lett. 2011, 13, 1881; c) S. Song, S.-F. Zhu, Y.-B. Yu, J.-L. Zhang, Angew. Chem. Int. Ed. 2013, 52, 1556; Angew. Chem. 2013, 125, 1596; d) E. N. Bess, M. S. Sigman, Organ. Lett. 2013, 15, 646.

[6] For examples of restricted rotation around C(sp²)–C(sp³) bonds, see: a) G. P. Newsorff, S. Sternhell, Tetrahedron Lett. 1967, 8, 2539; b) S. E. Boidadiev, D. A. Lightner, Monatsh. Chem. 2002, 133, 1469; c) H. Berber, P. Lameiras, C. Denz, C. Antheaume, J. Clayden, J. Org. Chem. 2014, 79, 6015; d) M. Flos, P. Lameiras, C. Denz, C. Mirand, H. Berber, J. Org. Chem. 2016, 81, 2372.

[7] The 'H NMR yields reported in Scheme 2 were extrapolated by integrating the major rotamer in the crude reaction mixture and applying a correction factor based on the 87:13 ratio of rotamers observed for the pure compound (see Supporting Information for details).

[8] For benzylamines without information for details).

[9] 1-iodo-3-methoxybenzene (3i) was used in place of iodo benzene (3a) in some examples as it facilitated purification, particularly from homocoupling product.
Communications

Cross-Coupling

B. Rubial, B. S. L. Collins, R. Bigler, S. Aichhorn, A. Noble, V. K. Aggarwal

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

The coupling of benzylamines, boronic esters, and aryl iodides gives 1,1-diaryalkanes with high stereospecificity through a one-pot sequential 1,2-metalate rearrangement/anti-S_N2' elimination/rearomatizing allylic Suzuki–Miyaura cross-coupling reaction.