Carbopalladation of C–C σ-bonds enabled by strained boronate complexes

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Abstract

Transition metal-catalysed cross-coupling reactions, particularly those mediated by palladium, are some of the most broadly used chemical transformations. The fundamental reaction steps of such cross-couplings typically include oxidative addition, transmetalation, carbopalladation of a π-bond, and/or reductive elimination. Herein, we describe an unprecedented fundamental reaction step: a C–C σ-bond carbopalladation. Specifically, an aryl palladium(II) complex interacts with a σ–bond of a strained bicyclo[1.1.0]butyl boronate complex to enable addition of the aryl palladium(II) species and an organoboronic ester substituent across a C–C σ-bond. The overall process couples readily available aryl triflates and organoboronic esters across a cyclobutane unit with total diastereocontrol. The pharmaceutically-relevant 1,1,3-trisubstituted cyclobutane products are decorated with an array of modular building blocks, including a boronic ester which can be readily derivatized.

Introduction

Transition-metal-catalyzed cross-couplings are one of the cornerstones of modern organic synthesis.[1] Due to their broad scope and ease-of-use, cross-coupling chemistry has been widely employed for the preparation of pharmaceuticals, functional materials, and agrochemicals. In particular, the pharmaceutical industry has used this strategy to combine readily available building blocks for the rapid synthesis of diverse libraries of compounds for biological evaluation.[2] However, there are limited ways in which organic molecules can interact with transition-metal centers, which restricts the compounds that can be prepared. Thus, enhancing reactivity modes of transition-metals has considerable translational

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potential, particularly if they enable the coupling of pre-existing building blocks to create new compound classes.[3]

The Suzuki–Miyaura reaction is arguably the most important cross-coupling because of its reliability and broad scope.[4] In general terms, the reaction sequence starts with an oxidative addition between an aryl halide and palladium(0), followed by a transmetalation with an organoboron reagent, and finally a reductive elimination to generate a new C–C bond (Figure 1a). In a twist on this venerable reaction, Morken replaced the traditional transmetallation step with a carbopalladation of a C–C π-bond of a vinyl boronate complex (Figure 1b).[5–9] Specifically, the C–C π-bond reacted with an electrophilic palladium(II) complex, resulting in a 'conjunctive' cross-coupling of a boronic ester and an aryl halide or triflate across a vinyl organometallic.

We wished to investigate whether the carbopalladation of a C–C σ-bond of a boronate complex was possible, as this would represent an entirely unprecedented fundamental transformation of both palladium and boronate complexes. However, whilst C–C π-bonds are well known to react with palladium complexes,[10] σ-bonds generally do not.[11] In order to weaken the σ-bond, and promote reaction with organometallic intermediates, we considered using ring strain, which can make σ-bonds begin to behave like π-bonds. The strategy of using strain-release[12,13] has recently emerged as a powerful tool to generate small, cyclic bioisosteric motifs, such as bicyclo[1.1.0]pentanes, azetidines, and cyclobutanes, resulting in a significant expansion of chemical space for drug discovery. In the context on transition-metal catalysis, the activation of highly strained C–C σ-bonds has been achieved,[14,15] but is generally limited to oxidative addition[16] and β-carbon elimination processes (e.g. the ring-opening of cyclopropylsilyl ethers[17] and cyclobutanols[18] to give alkyl ketones).

In this first instance, we aimed to exploit the bicyclo[1.1.0]butane (**1**) framework (Figure 1c),[19] which has the greatest strain energy (ca. 66 kcal/mol) of all fully saturated bicyclic carbocycles[20]. Bicyclo[1.1.0]butane (**1**) has received considerable interest, where its ring strain has previously been

harnessed to stimulate a variety of transition-metal-mediated rearrangements.[21,22] We therefore reasoned that if we could prepare a bicyclo[1.1.0]butyl boronate complex, with its weakened C–C σ-bond, the tendency of the boronic ester substituent to undergo 1,2-migration would provide sufficient 'push' to promote reaction with an electrophilic palladium-aryl complex at the β-carbon. This would result in 1,2-migration of the boron substituent to the α-carbon with simultaneous cleavage of the C–C σ-bond and formation of a C–Pd bond at the β-carbon. Such a process would constitute an unprecedented C–C σ-bond carbopalladation process. Reductive elimination will finally generate a high value borylated 1,1,3-trisubstituted cyclobutane product,[23] where two readily available building blocks, boronic esters and aryl halides, have been formally added across a C–C σ-bond. This proposal offers a mechanistically distinct method to prepare challenging polysubstituted cyclobutanes[24,25] with the potential to open up considerable chemical space due to the three readily diversifiable positions (aryl halide, boronic ester substituent, and the boron atom itself). In addition to their occurrence in numerous medicinally-relevant natural products and pharmaceuticals,[26–28] cyclobutanes are useful synthetic intermediates[29,30] and are of increasing interest in medicinal chemistry since they can act as rigid carbon scaffolds[31] and as sp^3-carbon rich bioisosteres of aromatic rings.[32,33] Indeed, the European Lead Factory,[34] which has been established to identify promising starting points for drug discovery, is searching for unique, synthetically tractable compound classes featuring rigid, non-planar scaffolds with two or more diversifiable regions, and substituted cyclobutanes have been identified as fulfilling these criteria.[35]

Results and discussion

We began our studies by directly generating 1-lithio bicyclo[1.1.0]butane **3** from 1,1-dibromo-2-(chloromethyl)cyclopropane **2** using Wipf's procedure[21] (Figure 1d). Whilst reaction of **3** with cyclohexyl pinacol boronic ester did indeed result in formation of the intermediate bicyclo[1.1.0]butyl boronate complex (as observed by ^{11}B NMR spectroscopic analysis of the reaction mixture), all attempts at subsequent cross-coupling were unsuccessful. We hypothesized that the presence of halide salts was deleterious to the subsequent cross-coupling since they can coordinate to palladium(II), making it less electrophilic.[6] We therefore considered using a sulfoxide as a latent organolithium, since the sulfoxide can

be isolated and purified, and the corresponding organolithium regenerated by treatment with *tert*-butyl lithium, free from halide salts, cleanly and quantitatively in just a few minutes.[36] Sulfoxide **5** was prepared by trapping 1-lithio bicyclo[1.1.0]butane **3** with sulfinate ester **4**, which, being crystalline, was easily purified and was isolated in 52 % yield on gram-scale (see supplementary section 2.2 for details). The sulfoxide-lithium exchange reaction of **5** was carried out in the presence of cyclohexyl pinacol boronic ester in 2-methyl tetrahydrofuran at −78 °C, to give the bicyclo[1.1.0]butyl boronate complex (Table 1). During optimization of the subsequent cross-coupling, we found that reaction of the boronate complex with phenyl triflate, catalyzed by a pre-formed complex of bis(dibenzylideneacetone)palladium(0) ($Pd(dba)_2$) and 1,1′-bis(diisopropylphosphino)ferrocene (dippf), at 40 °C for 14 hours was optimal for both reactivity and diastereoselectivity, leading to cyclobutane **6** in 77 % isolated yield and >98:2 dr (see supplementary section 3.1 for full details of optimization). The successful realization of the cross-coupling reaction, in stark contrast to its complete failure when we used the organolithium directly from 1,1-dibromo-2-(chloromethyl)cyclopropane, vindicated our choice of employing the sulfoxide as a convenient and clean source of the organolithium. As observed by Morken in reactions of vinyl boronates,[5] we found that aryl triflates performed considerably better than the corresponding bromides and iodides. It should be noted that the successful realization of our proposed reaction sequence demonstrates that addition of the palladium(II) complex to the strained σ-bond outcompetes transmetalation of the two C–B bonds.

Having established optimal cross-coupling conditions, we next investigated the scope of the two reaction partners. Using cyclohexyl pinacol boronic ester as a standard substrate, the scope of aryl triflates was explored and found to be broad, encompassing a wide range of electron-rich, electron-deficient and heteroaromatic triflates. In the case of electron-deficient aryl triflates, trifluoromethyl (**7**), fluoro (**8**), chloro (**9**), bromo (**10**) and ester (**11**) substituents worked well, but a nitro substituted aromatic triflate resulted in a low yield (**12**). In the case of electron-rich aryl triflates, methoxy (**13**) and dimethylamino (**14**) substituted aromatic triflates worked very well, as did the sterically encumbered 2,6-dimethyl substituted triflate (**15**). The reaction also tolerated a boronic ester substituent on the aryl triflate (**16**), which, like the bromo example (**10**), provides a useful handle for further coupling. Heterocyclic triflates,

including 2-pyridinyl (**17**) and 8-quinolinyl triflate (**18**) were also found to be excellent substrates. Cyclohexenyl (**19**) and vinyl (**20**) triflates also worked well, providing moderate to high yields of the corresponding cyclobutanes.

The scope of the boronic ester was then explored, using phenyl triflate as a standard substrate, and was found to be similarly broad. Primary, secondary, and tertiary boronic esters could all be employed, showing that the reaction tolerated the full spectrum of steric demand. Notably, methyl, which is generally a poor migrating group[37] and has even been used as a non-migrating group, gave a good yield of the corresponding cyclobutane (**21**). Given the importance of methyl groups in biologically-relevant molecules,[38] this reaction was performed on gram-scale in similarly good yield. In the case of secondary boronic esters, an enantioenriched boronic ester (**24**) migrated with complete stereospecificity. Cyclopropyl (**25**) and benzylic substituents (**26**) also performed well, as did α-heteroatom substituted boronic esters, including N-boc 2-piperidine (**27**) and an α-alkoxy boronic ester (**28**). The tertiary boronic esters tested included adamantyl (**29**), *tert*-butyl (**30**), and a functionalized cubyl moiety (**31**), all of which performed well in the coupling. A broad range of aromatic and heteroaromatic boronic esters were also successfully employed (**34**–**39**). An N-boc tetrahydropyridine (**32**) and a vinyl boronic ester (**33**) were also effective substrates, furnishing the unsaturated cyclobutanes in good yield. The latter example is especially noteworthy since the intermediate boronate complex could react with the electrophilic palladium(II) complex at the π-bond (Morken's conjuctive cross-coupling reaction, Figure 1b)[5–9] or at the strained σ-bond of the bicyclo[1.1.0]butane. Since we observed exclusive formation of cyclobutane **33**, reaction of the palladium(II) complex at the σ-bond must be considerably faster than at the π-bond, which is a remarkable finding.

To explore the scope and functional group tolerance even further, we tested a range of structurally complex natural product-derived triflates and boronic esters (Figure 2a). These included derivatives of eugenol (**41**), estrone (**42**), tyrosine (**44**), pregnenolone (**45**), and cholesterol (**46**), which in all cases were transformed into the cyclobutane derivatives in moderate to good yields. However, a triflate with an

acidic N–H was not successful, since the boronate complex was protonated instead of reacting with the palladium(II) complex (see supplementary section 4.12).

Boronic esters are invaluable building blocks for the synthesis of pharmaceuticals, agrochemicals, and materials, because they can be easily transformed into a broad range of other functional groups.[39] Since our cyclobutane products retain this moiety, we wanted to showcase that they too could be easily functionalized (Figure 2b). Therefore, biologically-relevant methyl substituted boronic ester **21** was oxidized to the corresponding alcohol (**47**). We also demonstrated arylations to form a furan[40] and pyridine[41] (**48**, and **49**), amination[6] (**50**), vinylation[42] (**51**), alkynylation[43] (**52**), and formation of the trifluoroborate salt[44] (**53**), the last four of which incorporate highly versatile functional handles that could enable further diversification of the cyclobutane scaffold.[45] Furthermore, boronic ester **35** could also undergo protodeboronation[46] to produce 1,3-disubstituted cyclobutane **54**. In all cases, good to excellent yields were obtained with complete retention of stereochemistry, demonstrating the power of the methodology to enable the rapid preparation of a range of highly functionalized cyclobutanes, including those featuring all-carbon quaternary centers.

In all cases explored, the cyclobutanes were formed as single diastereomers, as judged by ^{1}H NMR spectroscopic analysis (on both the crude mixtures and purified products). Single crystals of **7**, **15** and **35** were obtained and subjected to X-ray crystallographic analysis, which unambiguously proved that the boron- and triflate-bearing groups were incorporated onto the same face of the cyclobutane ring. All other cyclobutane products in Table 1 and Figure 2 were assigned by analogy. The reaction pathway and selectivity can be plausibly rationalized by the following mechanism (Figure 3). Oxidative addition of the triflate generates an electrophilic palladium(II) complex with a vacant coordination site which can interact with the boronate complex. Boronate complexes normally undergo transmetalation at the α-carbon, but this reactivity is not observed under our conditions. Instead, the ring strain of the bicyclo[1.1.0]butane moiety transmits the nucleophilicity of the boronate complex (**55**) to the β-carbon, so reaction at this position with the electrophilic palladium(II) complex is favored. At the β-carbon,

reaction can occur on either the *exo* or the *endo* face. However, since an anti-periplanar alignment of the migrating substituent R^1 and the central C–C bond of the bicyclo[1.1.0]butane unit is required for 1,2-metalate rearrangement,[47,48] boronate complex **55** reacts in the conformation shown in Figure 3. Approach of the bulky palladium(II) complex from the *endo* face is therefore blocked by the large pinacol group. In addition, since the central C–C bond of the bicyclo[1.1.0]butane unit is largely formed from unhybridised 2p-orbitals, there is significant electron density on the *exo* face of the β-carbon,[47,48] which can interact with the vacant coordination site on the electrophilic palladium(II) complex. Therefore, both steric and electronic factors favor coordination between the nucleophilic β-carbon and the electrophilic palladium(II) complex on the *exo* face of the bicyclo[1.1.0]butane. This coordination induces a 1,2-metalate rearrangement. Here, R^1 migrates to the α-carbon with simultaneous cleavage of the highly strained C–C σ-bond and formation of a new C–Pd bond at the β-carbon. Whilst most transmetalation events occur with retention of configuration,[49] here we observe inversion of configuration at the β-carbon, a process which has occasionally been reported.[50-53] The overall process constitutes a carbopalladation of a C–C σ-bond, albeit a highly strained one, which is an unusual and unprecedented process. Strain-release provides a significant driving force. Indeed, a less strained cyclopropyl boronate complex (strain energy: 29 kcal/mol)[13] did not react under our optimized conditions (see supplementary section 6.2). Finally, reductive elimination affords the sp^2–sp^3 coupled product and regenerates palladium(0) to complete the catalytic cycle. The overall result is a distal sp^2–sp^3 cross-coupling, where the two reaction partners are coupled diastereoselectively across a cyclobutane unit.

Conclusions

We have described a strategy in which two of the most readily available classes of building blocks, aryl triflates and boronic esters, can be coupled with a cyclobutane motif sandwiched between them, opening up significant chemical space. The synthesis and use of the novel bicyclo[1.1.0]butyl sulfoxide (**5**), an easily accessible reagent, was critical to the success of the transformation; it acted as a linchpin, bringing together the two building blocks across a cyclobutane in a fully diastereoselective manner. The methodology enables the modular synthesis of rigid 1,1,3-trisubstituted cyclobutanes, which could act as

three-dimensional scaffolds for the presentation of functional groups in any desired vector. Furthermore, the retention of the boronic ester significantly enhances the versatility of the chemistry since it can be transformed into a range of functional groups. Perhaps most importantly, this process unveils a fundamental new reactivity mode of palladium complexes: the carbopalladation of σ-bonds. It is anticipated that this unprecedented reactivity mode will be applicable in other well-established cross-coupling methodology and therefore enable access to unchartered chemical space.

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Data availability

The authors declare that the data supporting the findings of this study are available within the paper and its supplementary information files. Crystallographic data for compounds **5, 7**, **15** and **35** are available free of charge from the Cambridge Crystallographic Date Centre (www.ccdc.cam.ac.uk) under reference numbers 1835072, 1847415, 1835073, and 1847416, respectively.

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Author Contributions

V.K.A. and A.F. conceived the project. A.F. designed and conducted the experiments and analysed the data. T.B. first synthesised compound **5**. V.K.A. and A.F. prepared the manuscript.

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Competing interests

The authors declare no competing interests.

Figure 1. Previous palladium-mediated cross-coupling reactions involving organoboron reagents, and our reaction design. a, The Suzuki–Miyaura cross-coupling reaction proceeds via transmetalation of an aryl palladium(II) complex with an aryl boronic acid to ultimately form a biaryl product. **b**, Morken's conjunctive cross-coupling enables the addition of an organoboronic ester substituent and an aryl triflate across the C–C π-bond of a vinyl group. The aryl palladium(II) complex-induces a 1,2-metalate rearrangement, where the organoboronic ester substituent and the aryl palladium(II) complex are added across the C–C π-bond (π-bond carbopalladation).[5-9] **c**, Our proposed C–C σ-bond carbopalladation process. A highly strained bicyclo[1.1.0]butyl boronate complex (strain energy: 66 kcal/mol) is proposed to undergo an aryl palladium(II) complex-induced 1,2-metalate rearrangement, where the organoboronic ester substituent and the aryl palladium(II) complex are added across the central C–C σ-bond of the bicyclo[1.1.0]butyl unit to ultimately form a highly valuable cyclobutane product. **d**, Initial unsuccessful attempt at cross-coupling bicyclo[1.1.0]butyl boronate complexes formed from 1,1-dibromo-2-(chloromethyl)cyclopropane due to the inhibitory effect of halide anions. Synthesis of sulfoxide **5**, which is a crystalline, easy-to-handle precursor to halide-free 1-lithio bicyclo[1.1.0]butane **3**. a) Et_2O, –78 °C, MeLi, 30 min, then –50 °C, 1 h; b) –78 °C, *t*BuLi, 20 min; c) –78 °C, $MgBr_2 \bullet Et_2O$, 2 h; d) **4**, –78 °C, 5 min, then ambient temperature, 30 min.

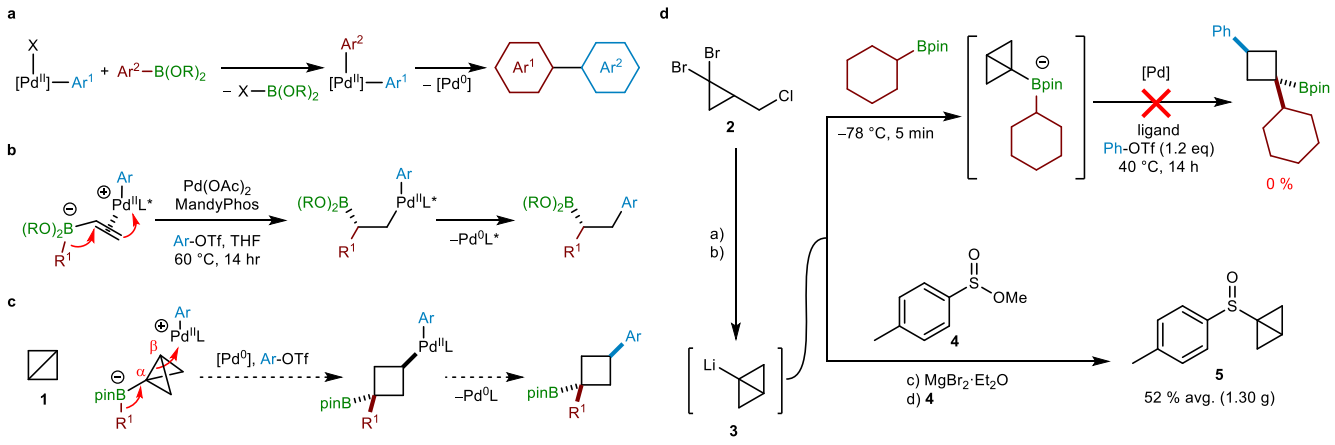


Figure 2. Applications of the distal cross-coupling reaction. a, Natural product-derivatives scope. **b**, Boronic ester functionalizations. Isolated yields are reported. ^{1}H NMR spectroscopy of crude reaction products was used to assess diastereoisomeric ratios (d.r.). Simplified reaction conditions: a) $NaOH/H_2O_2$; b) ArLi, then *N*-bromosuccinimide; c) ArLi, then 2,2,2-trichloroethyl chloroformate, then $NaOH/H_2O_2$; d) $MeONH_2$, KO^tBu, then Boc_2O; e) vinylmagnesium chloride, then I_2, then NaOMe; f) vinyl diisopropylcarbamate, LDA, then I_2, then LDA, then acetone; g) KHF_2; h) TBAF.xH_2O.

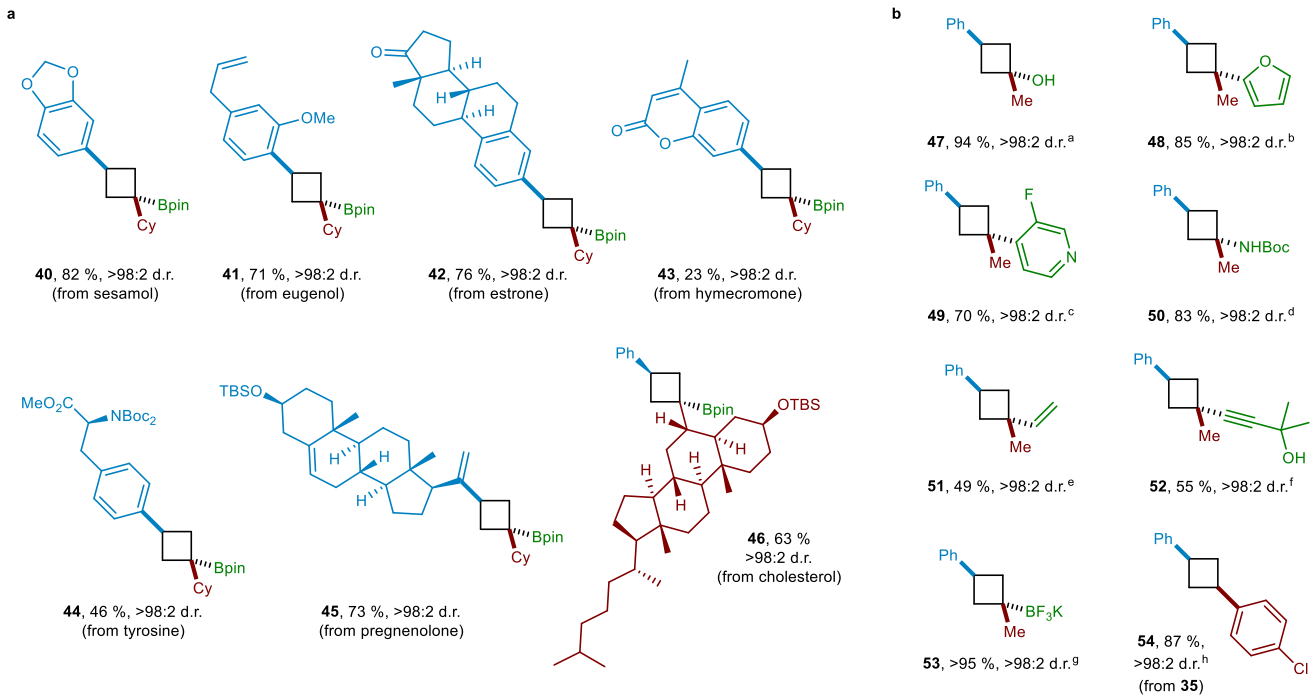


Figure 3. Proposed catalytic cycle for the distal cross-coupling. The mechanism begins with an oxidative addition between a palladium(0) complex and the aryl triflate to give an aryl palladium(II) intermediate. Boronate complex **55** reacts in the conformation shown to satisfy the antiperiplanar requirement of the 1,2-migration process of R^1 to the α-carbon. This means that the aryl palladium(II) complex must approach **55** from the *exo* face of the bicyclo[1.1.0]butyl unit because approach from the *endo* face is restricted due to steric clash with the bulky pinacol group. Furthermore, since the central C–C σ-bond of the bicyclo[1.1.0]butyl unit is comprised of unhybridized 2p-orbitals, significant electron density protrudes from the *exo* face which can interact with the aryl palladium(II) complex. Interaction of **55** with this complex induces a 1,2-metalate rearrangement, where there is simultaneous 1,2-migration of R^1 to the α-carbon, cleavage of the central C–C σ-bond, and formation of a C–Pd bond at the β-carbon (a C–C σ-bond carbopalladation). Finally, reductive elimination yields the arylated cyclobutane product and regenerates the palladium(0) complex.

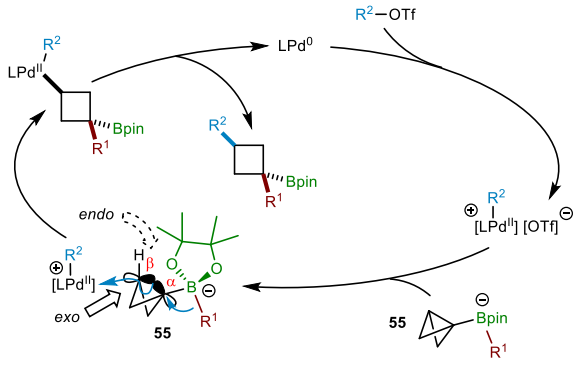
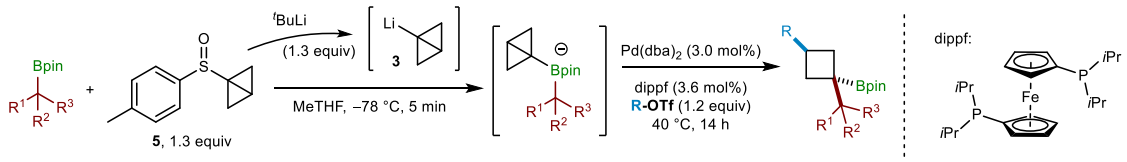
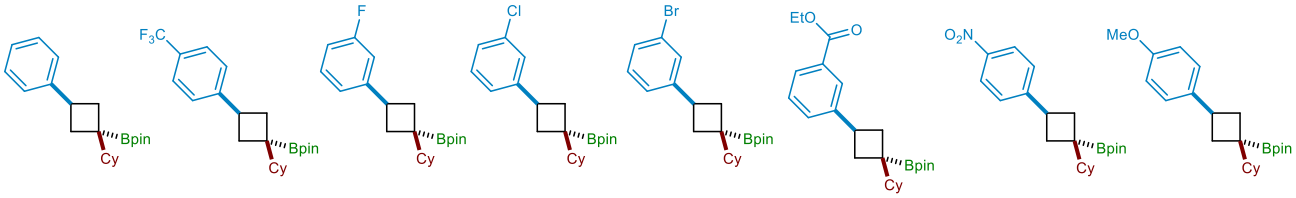


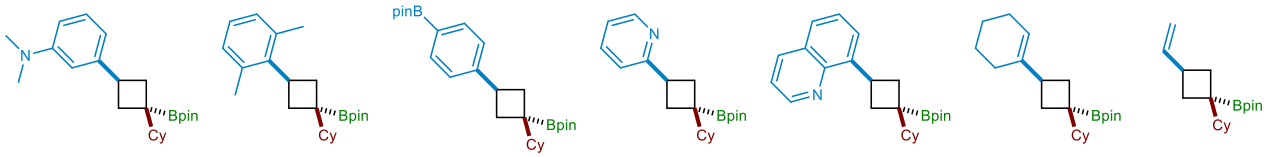
Table 1. Boronic ester and triflate scope.



Triflate scope

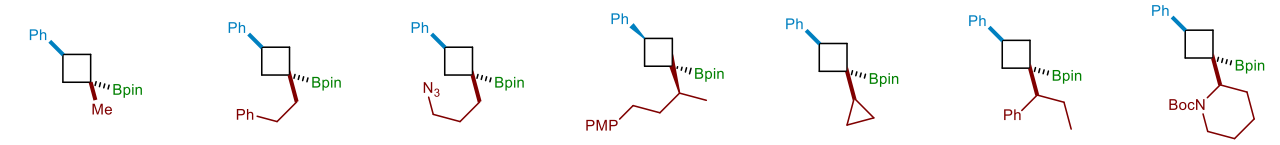


6, 77 %, >98:2 d.r. **7**, 77 %, >98:2 d.r. **8**, 78 %, >98:2 d.r. **9**, 81 %, >98:2 d.r. **10**, 62 %, >98:2 d.r. **11**, 47 %, >98:2 d.r. **12**, 10 %, >98:2 d.r. **13**, 81 %, >98:2 d.r.

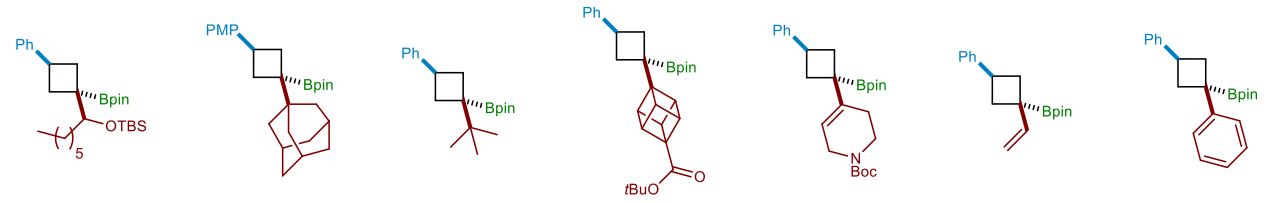


14, 89 %, >98:2 d.r. **15**, 66 %, >98:2 d.r. **16**, 58 %, >98:2 d.r. **17**, 74 %, >98:2 d.r. **18**, 86 %, >98:2 d.r. **19**, 78 %, >98:2 d.r. **20**, 55 %, >98:2 d.r.

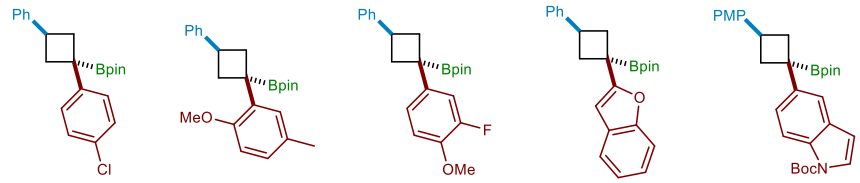
Boronic ester scope



21, 62 %, >98:2 d.r.
58 %, >98:2 d.r. (1.12 g)
22, 76 %, >98:2 d.r. **23**, 20 %, >98:2 d.r. **24**, 77 %, >98:2 d.r., 100 % e.s. **25**, 85 %, >98:2 d.r. **26**, 78 %, >98:2 d.r. **27**, 51 %, >98:2 d.r.



28, 65 %, >98:2 d.r. **29**, 57 %, >98:2 d.r.* **30**, 69 %, >98:2 d.r. **31**, 40 %, >98:2 d.r. **32**, 52 %, >98:2 d.r. **33**, 61 %, >98:2 d.r. **34**, 70 %, >98:2 d.r.



35, 67 %, >98:2 d.r. **36**, 64 %, >98:2 d.r. **37**, 59 %, >98:2 d.r. **38**, 35 %, >98:2 d.r. **39**, 26 %, >98:2 d.r.*

Boronic ester (0.24 mmol, 1.0 equiv), **5** (60 mg, 0.31 mmol, 1.3 equiv) and *t*BuLi (0.31 mmol, 1.3 equiv) in 2.1 mL MeTHF at –78 °C for 5 min, then addition of $Pd(dba)_2$ (4.1 mg, 3.0 mol%) and dippf (3.6 mg, 3.6 mol%) (pre-mixed in 0.5 mL MeTHF for 20 min) and the triflate (0.29 mmol, 1.2 equiv), and heated at 40 °C for 14 h. Isolated yields are reported. ^{1}H NMR spectroscopy of crude reaction products was used to assess diasteroisomeric ratio (d.r.). **para*-Methoxyphenyl triflate was used in place of phenyl triflate.