On the total synthesis of terpenes containing quaternary stereocenters
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Pd-catalyzed Asymmetric Conjugate Addition of Ortho-substituted Arylboronic Acids to Cyclic β-substituted Enones

**ABSTRACT:** In 2012 our laboratory developed the Pd-catalyzed asymmetric conjugate addition of arylboronic acids to cyclic β-substituted enones. Despite the success of the methodology ortho-substituted arylboronic acids were not tolerated in the reaction, limiting its scope. Our recent efforts, highlighted in this chapter, focused on the optimization of the catalytic system to allow reaction with ortho-substituted arylboronic acids, creating a sterically congested quaternary stereocenter. The methodology can potentially be applied in the total synthesis of several natural products, of which herbertenediol and enokipodin A and B were chosen as synthetic targets. This research also set the stage for a short asymmetric total synthesis of the symmetrical biaryl natural product mastigophorene A.

CHAPTER 5

5.1 Introduction

The catalytic asymmetric construction of quaternary stereocenters is widely regarded as one of the major challenges in synthetic organic chemistry.\(^{[1]}\) One efficient strategy to achieve this goal is the conjugate addition of carbon nucleophiles to \(\beta,\beta\)-disubstituted unsaturated carbonyl compounds.\(^{[2]}\)

Employing asymmetric copper catalysis, the groups of Alexakis, Fillion and Hoveyda successfully added trialkylaluminum, dialkylzinc and alkyl Grignard reagents to a variety of \(\beta,\beta\)-disubstituted unsaturated electrophiles.\(^{[3]}\) Though addition of the corresponding arylationuminum and arylzinc reagents was feasible, the general use of aryl Grignard reagents is still problematic due to their high reactivity. Moreover, the use of ortho-substituted aryl groups (either in the \(\beta,\beta\)-disubstituted unsaturated electrophile or in the organometallic reagent) is precarious, generally leading either to failure of the reaction, or low to moderate ee.\(^{[3q,r,v,y]}\) A notable exception has been reported by Hoveyda and co-workers who obtained excellent enantioselectivities (>95%) with anisole and \(o\)-tolyl aluminum reagents.\(^{[3s]}\) Alternatively, rhodium-catalyzed conjugate addition of organoboron reagents, developed by Hayashi and co-workers, has been employed, but also in these systems the use of ortho-substituted arylboronic acids is very limited.\(^{[4,5]}\)

In 2011, the Stoltz laboratory reported the first asymmetric palladium-catalyzed conjugate addition of arylboronic acids to cyclic \(\beta,\beta\)-disubstituted enones using \(t\)BuPyOx as the ligand.\(^{[6]}\) Shortly thereafter we reported the asymmetric Michael addition of arylboronic acids to cyclic \(\beta,\beta\)-disubstituted enones and lactones, catalyzed by \(\text{PdCl}_2\)-PhBOX (Scheme 1).\(^{[7]}\) Both systems showed high enantioselectivities, high yields, broad functional group tolerance, mild reaction conditions and a considerable scope in both the cyclic Michael acceptor and the arylboronic acid. In addition, in both systems the reactions can be carried out in air. However, to date, the successful application of a broad range of ortho-substituted arylboronic acids has not been reported,\(^{[8]}\) although the Stoltz laboratory managed the asymmetric conjugate addition of \(o\)-fluoro arylboronic acid to 3-methyl cyclohex-2-enone in an enantiomeric excess of 77%. A quaternary center vicinal to an ortho-substituted phenyl ring is a very congested situation indeed.

Very recently, Sigman and co-workers reported the asymmetric Pd-catalyzed remote benzylic quaternary stereocenter formation using arylboronic acids.\(^{[9]}\) A broad substrate scope, consisting exclusively of linear substrates, was reported with very good to excellent enantioselectivities (86-98% ee), and yields generally ranging from 50 to 80%. However, when using the ortho-substituted \(o\)-tolyboronic acid and dibenzofuran-4-boronic acid the yields dropped significantly to 35% and 25% respectively, showing the problems associated with ortho-substitution.
Pd-catalyzed Asymmetric Conjugate Addition of Ortho-substituted Arylboronic Acids

Scheme 1. The current state of the art (up to April 2014) in Pd-catalyzed asymmetric Michael additions to create benzylic quaternary stereocenters.

Asymmetric synthesis of benzylic quaternary centers with ortho-substitution is desired, since many natural products bear such a moiety, several of which are presented in Scheme 2. We also envision this transformation beneficial in the sense that direct installation of the ortho-substituted benzylic stereocenter can significantly shorten synthetic endeavors to such natural products.

Here, we present the palladium-catalyzed conjugate addition of ortho-substituted arylboronic acids to β-methyl substituted cyclic enones, both in an asymmetric and a racemic fashion. The developed methodology is applied in the total synthesis of the stercally congested, biologically active, sesquiterpenes herbertenediol and enokipodin A and B.
5.2 Development of the asymmetric Pd-catalyzed conjugate addition of ortho-substituted arylboronic acids to β,β-disubstituted cyclic enones

In a recent report,\textsuperscript{[10]} we showed efficient conjugate addition to cyclic β-substituted enones employing 1 mol% of a \( \text{Pd(CF}_3\text{CO}_2\text{)}_2/2\text{,2-bipyridine catalyst, two equivalents of boronic acid, at 60 °C for 18 h.} \) Under these conditions the use of ortho-substituted arylboronic acids was fruitless, leading only to trace amounts of product. It was reasoned, however, that increasing the catalyst loading from 1 mol% to 5 mol%, extending the reaction time and changing the stoichiometry of the reaction (7 equivalents of enone instead of 2 equivalents of boronic acid)\textsuperscript{[11]} could change this situation. This indeed proved to be the case, and a wide range of ortho-substituted arylboronic acids could be employed in the conjugate addition (Scheme 3).

\textbf{Scheme 3.} Racemic Pd-catalyzed conjugate addition of ortho-substituted arylboronic acids to β-methyl cyclic enones. \textsuperscript{a} Double catalyst loading.
As evident from Scheme 3, the Michael additions to 3-methyl cyclopent-2-enone generally gave satisfying results. As expected, an increase in the steric bulk of the ortho-substituent led to diminished yields, but in the case of the relatively small ortho-fluoro and ortho-chloro arylboronic acids low yields were obtained as well (20% and 12% respectively for 3c and 3d). These low yields might be attributed to electronic effects, thus in order to achieve acceptable yields for these substrates the catalyst loading was doubled to 10 mol% leading to 51% and 31% isolated yield for ortho-fluoro and ortho-chloro phenylboronic acid, respectively.

With these results in hand, we expanded the reaction scope in the Michael acceptor to 3-methyl cyclohex-2-enone. In all cases the isolated yields significantly dropped, though ortho-methyl, ortho-methoxy, and 2-methoxy-5-methyl phenylboronic acid (see 4a, 4b and 4i) gave acceptable yields (41%, 55% and 63% respectively). In contrast with 3-methyl cyclopent-2-enone, doubling of the catalyst loading did not always result in significantly better yields. In the case of ortho-chloro phenylboronic acid (see 4d) only 8% of the desired product was isolated after two days of reaction, which clearly indicates the limits of this approach.

The conjugate addition of ortho-substituted arylboronic acids to 3-methyl cyclohept-2-enone was shortly investigated but did not lead to yields over 10% using 8 mol% of catalyst. This result is surprising to us since in our previously reported system, 3-methyl cyclohept-2-enone was tolerated as a substrate (using phenylboronic acid). Since no electronic reasons can be given to describe the failure of the reaction, we attribute this to steric hindrance.

With the Michael addition of ortho-substituted arylboronic acids to cyclic β-disubstituted enones accomplished, we had the ambition to develop an asymmetric variant of this transformation using our previously developed catalyst. This reaction is expected to be significantly more challenging since steric interactions are more pronounced in enantioselective catalysis. Initial studies using o-tolylboronic acid, employing 15 mol% of catalyst PdCl$_2$-PhBOX, and 40 mol% AgSbF$_6$ at 60 °C, clearly showed this was the case since the impurity profile of the reaction was dominated by homo-coupling of the arylboronic acid. Therefore we set out to optimize the reaction to reduce this unwanted side product (Table 1).
Table 1. Optimization of the reaction conditions in the conjugate addition of ortho-tolylboronic acid to β-methyl cyclopentenone.

Lewis acid activation of the enone increases its reactivity as a Michael acceptor. The use of 40 mol% of either Mg, Zn, Fe or Cu triflate gave negligible results and therefore the stronger coordinating rare-earth metal triflates Sc(OTf)₃, Yb(OTf)₃, In(OTf)₃, and Ce(OTf)₃ were applied. A slight enhancement of the product versus homo-coupling ratio was observed but still the reaction was greatly in favor of the latter. Homo-coupling of arylboronic acids is generally observed using Pd-catalysis, and can be counter-balanced by changing the stoichiometry of the reaction, applying the reaction partner in excess. As β-methyl cyclopentenone and β-methyl cyclohexenone are less expensive than most arylboronic acids, this is an attractive approach. Using three equivalents of enone, the product ratio changed to 1.5 : 1 in favor of the Michael adduct. A further enhancement to 2 : 1 was observed using five equivalents of enone and ultimately a 2.5 : 1 ratio was found using 1.2 equivalents. During this optimization process, Stoltz and Houk reported a mechanistic investigation of the Pd-catalyzed asymmetric Michael addition of arylboronic acids to enones. It was shown that the chemical yields previously obtained, could be enlarged by adding...
NH$_4$PF$_6$ (30 mol%) and water (5 eq) to their system. We adopted these conditions by changing the solvent from MeOH/H$_2$O to dichloroethane, and the silver salt from AgSbF$_6$ to AgCF$_3$CO$_2$ to obtain a similar system, still using 7 eq of the enone.[13] This proved to be highly beneficial for the formation of the Michael adduct since the product ratio dramatically increased to 20:1. With this result in hand, the catalyst loading was lowered to 8 mol% leading to a slight decrease of the product ratio (18:1). Further reduction to 4 mol% of catalyst resulted in a respectable 12:1 ratio in favor of the Michael adduct, however at the cost of longer reaction times. Finally we also attempted to reduce the number of additives (AgCF$_3$CO$_2$ and NH$_4$PF$_6$) by combining them in the form of AgPF$_6$. Surprisingly, this led to an unaccountable lowering of the product ratio to 3.5:1.

With the reaction conditions optimized, the scope of the reaction was studied (Scheme 4). An immediate observation was that very good to excellent enantioselectivities were obtained, albeit that the isolated yields were moderate, and in some cases low. For some reactions (see 4b, 4c, 3f, 3i and 3j), due to the initially low isolated yield, the catalyst loading was doubled. This led, as expected, to an approximate doubling of the yield. Interestingly, in some cases (see 3f vs. 4f, 3h vs. 4h, 3i vs. 4i and 3k vs. 4k) addition to 3-methyl cyclohex-2-enone gave higher yields than addition to 3-methyl cyclopent-2-enone. These results are in contrast to the conjugate addition reactions with the bipyridine system (Scheme 3). It is also notable that the conjugate additions to 3-methyl cyclohex-2-enone give equal or higher enantiomeric excesses (up to 22% ee higher, see 3k vs. 4k) than the additions to 3-methyl cyclopent-2-enone.
The general observation that the yields are higher, and ee’s are lower, for conjugate additions to cyclopentenone compared to cyclohexenone are speculated to be the consequence of steric hindrance. The chiral environment of the catalyst allows “easy” access of the cyclopentenone (faster reaction, higher yield) but with a decreased facial bias (lower ee). On the other hand, cyclohexenone does not enter the chiral environment of the catalyst that easily (slower reaction, more protodeboronation) but when it does, it does so with an increased facial bias.

The moderate yields were found to result from significant protodeboronation of the boronic acids. According to literature, this side reaction can be attributed to multiple factors, especially when taken into account the low reaction rate of the asymmetric Michael addition. Given the conditions of the conjugate addition, protodeboronation\(^{16a, 12b}\) might be associated with: 1) Pd-catalyzed protodeboronation\(^{16c}\) 2) Ag-catalyzed protodeboronation\(^{16d-k}\) 3) heat-induced protodeboronation\(^{16l}\) 4) fluoride-mediated protodeboronation (with PF\(_6^-\) as a potential F\(^-\) source)\(^{16m}\) 5) acid-catalyzed protodeboronation\(^{16m-o}\) and finally 6) water-induced protodeboronation.\(^{16p}\) It is likely that more than one of these factors plays an important role here but we were not able to suppress this unwanted side reaction.\(^{17}\)

That the moderate yields obtained here do not stand out, is apparent from a recent report by the Sigman group, as discussed earlier.\(^{19}\) For their asymmetric Pd-catalyzed remote benzylic quaternary stereocenter formation using arylboronic acids, the yields are typically 50-80%, however when using o-tolybloronic acid and dibenzofuran-4-boronic acid the yields dropped significantly to 35% and 25% respectively.

Despite significant protodeboronation, the substrate scope is respectable, although some ortho-substituted arylboronic acids and functionalized enones failed to react (Figure 1). It is not surprising that larger ortho-substituents such as CHO, NO\(_2\), CF\(_3\), iPr and CO\(_2\)Me impeded the reaction. In addition, di-ortho substitution was not tolerated. Variation of the five-membered enone in terms of substitution at the \(\alpha\)- or \(\gamma\)-position also led to failure of reaction, as did substituting the \(\alpha\)'-position of 3-methyl cyclohex-2-enone with a geminal dimethyl moiety.

![Figure 1. Unreactive substrates and boronic acids in the Pd-catalyzed asymmetric Michael addition.](image-url)
5.3 The shortest asymmetric total syntheses of herbertenediol and enokipodin A and B

Being able to construct the sterically very congested motif of an ortho-substituted arene connected to a quaternary stereocenter created the opportunity for the asymmetric total synthesis of the biologically active natural products herbertenediol, enokipodin A, and B. Herbertenediol is a sesquiterpene isolated from the liverworts Herberita aduncus[18] and Radula perrottetii,[19] and has been subjected to biological studies, which showed potent anti-lipid peroxidation activity in rat brain homogenates (100% inhibition at 1 μg/mL).[20] To date, seven (!) asymmetric syntheses of herbertenediol have been reported,[21] with the shortest route reported by Abad and co-workers[21d] comprising ten linear steps. Here the quaternary stereocenter was introduced by means of substrate control, as in the approach of Lin[21e] and Kita et al.[21g] The Bringmann laboratory employed a kinetic resolution,[21b] as did the Monti group,[21h] to furnish enantiopure material. Meyers[21a] and Fukuyama[21c] relied on the use of a chiral auxiliary. We reasoned that direct introduction of the quaternary stereocenter by means of an asymmetric conjugate addition of a suitable substituted phenylboronic acid allowed to shorten the synthesis of herbertenediol considerably.

The synthesis of herbertenediol started with the asymmetric conjugate addition of 2,3-dimethoxy-5-methyl phenylboronic acid 2g to 3-methyl cyclopentenone employing 8 mol% of PdCl₂-PhBOX, and afforded the desired Michael adduct 5 in 55% yield and high enantioselectivity (92% ee, Scheme 5). In order to selectively install the geminal dimethyl moiety without generating (hard to separate) regioisomers, 3g was subjected to an oxidative dehydrogenation. Initially, several stoichiometric oxidation procedures (DDQ,[22] IBX,[23] and iodic acid[24]) were applied, which led to low isolated yields (<30%) and over-oxidized products.[25] A suitable alternative was found in the Pd(CF₃CO)₂/4,5-diazafluorenone L1 catalyzed oxidation, recently developed by Stahl and co-workers.[26] Stahl reported cyclopentenone oxidation with oxygen (7.2 bar, 9% in N₂) using 5 mol% of catalyst, whereas catalyst decomposition was observed at atmospheric pressure. Also in the current case, oxidation of 3g at atmospheric pressure led to catalyst decomposition and only 15% conversion (GC-MS) was observed after 12 and 24 h. For practical reasons we decided to increase the catalyst loading to 40 mol%, at atmospheric oxygen pressure, which yielded 79% of enone 5.
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Scheme 5. A short asymmetric total synthesis of herbertenediol.

With 5 in hand, a one-pot geminal dimethylation as described by Srikrishna was employed yielding 77% of 6.[27] In order to acquire fully reduced product 7, several procedures were considered. Deoxygenation by means of a classic Wolff-Kishner reduction was reported to be problematic in related systems and was therefore rejected.[23] Deoxygenation employing a Mozingo reduction (thioketalization/Raney nickel desulfurization with the saturated analogue of 6) also has been reported to be problematic,[21a] although it was successfully applied recently in a very similar system.[27] To clarify these contradicting literature reports we performed the reaction under similar conditions as reported.[27] In our hands the reaction proved to be extremely slow and prone to side product formation, leading to an inseparable mixture of mainly oligomeric products, and only minor amounts of desired product. This observation is in line with a very recent report by Yoshida and co-workers, who also encountered reproducibility issues.[29] Alternatively, Meyers and co-workers described a reduction protocol in which 6 was converted into the corresponding thioketone and was subsequently reduced with Raney nickel (Ra/Ni), leading to 7 in 58% yield over the two steps.[21a] This strategy proved to be reproducible in our hands, providing us with 7 in 65% yield. An important, previously not reported, observation was that freshly prepared Ra/Ni had to be used for reproducible results. with commercial Ra/Ni, the reaction did not provide the desired product. This is likely due to the high activity of freshly prepared Ra/Ni (in which H₂ is adsorbed on the catalyst) compared to commercial Ra/Ni (no absorbed H₂ for safe shipment). Demethylation using BBr₃ then furnished herbertenediol in 82% yield, in a total of six steps, the shortest asymmetric synthesis to date.[30]

In 2000, the sesquiterpenes enokipodin A and B were isolated from the culture broth of the edible mushroom “enokidake” (Flammulina velutipes).[31] It was found that these
oxidized α-cuparenone-type compounds possess antimicrobial activity against *Cladosporium herbarum* and *Bacillus subtilis*.\(^{[32]}\) However, it is mainly their sterically congested structure that has attracted the synthetic community to embark on asymmetric syntheses of these molecules.\(^{[33]}\) Two of the three endeavors produced enokipodin B in a longest linear sequence of eleven steps, and one additional step for the enokipodin A synthesis. Kuwahara’s approach was based on the use of a chiral auxiliary\(^{[33c,d]}\) whereas Yoshida installed the quaternary stereocenter by substrate control.\(^{[33b]}\) In the most recent, ten step formal, enokipodin B synthesis, Hoveyda directly installed the benzylic quaternary center using an elegant multicomponent Ni-, Zr-, and Cu-catalyzed strategy.\(^{[33a]}\)

Our synthesis of enokipodin A and B started with the asymmetric Michael addition of boronic acid 2j to 3-methyl cyclopent-2-enone, yielding 3j in 21% yield and a good enantioselectivity of 74% ee (Scheme 6). Introduction of the α,β-unsaturation was subsequently achieved using the previously described Pd(CF₃CO₂)₂/4,5-diazafluorenone catalyzed oxidation, in 54% yield. Dimethylation followed by hydrogenation of enone 9 gave ketone 10 (60% yield over two steps), a common synthetic intermediate to access the desired natural products. Indeed, enokipodin A and B were both readily obtained in just one step, from 10 by either a cerium ammonium nitrate oxidation, leading to enokipodin B in 84% yield, or a BBr₃ mediated demethylation, providing enokipodin A in 57% yield. Though not the synthesis with the highest enantiomeric excess, we did manage to reduce the longest linear sequence from ten (enokipodin B) and eleven (enokipodin A) to only five steps.

Scheme 6. Asymmetric total synthesis of enokipodin A and enokipodin B.
5.4 Conclusion

In summary, we successfully incorporated ortho-substituted arylboronic acids in both the non-stereoselective as well as the asymmetric Pd-catalyzed Michael addition to β-disubstituted cyclic enones. In the non-stereoselective reaction, good yields are generally obtained with 3-methyl cyclopent-2-enone as the substrate and moderate yields with 3-methyl cyclohex-2-enone. In the asymmetric reaction, very good to excellent enantioselectivities are obtained, although yields stay moderate. Nevertheless, based on this method, the asymmetric total synthesis of the biologically active sesquiterpenes herbertenediol (92% ee), enokipodin A and enokipodin B (74% ee) was achieved with routes that are considerably shorter than previously reported.

5.5 Discussion and outlook

The development of this catalytic methodology originated from the idea to embark on the shortest asymmetric total synthesis of mastigophorene A and B (see chapter 6). The reaction served its purpose in the total synthesis of herbertenediol, the monomeric unit of the mastigophorenes A and B. However, when reflecting on our efforts to achieve an efficient catalytic method, we do need to address the problems associated with the low to moderate isolated yields. As shown in this chapter the original catalytic procedure for conjugate addition to cyclic 3-methyl enones (Scheme 1),[7] had to be drastically altered in order to produce the desired products. We did however struggle in gaining control over unwanted protodeboronation of the arylboronic acid. In retrospect, changing the original reaction medium (MeOH/H$_2$O 4:1) to dichloroethane also provides the opportunity to re-investigate[7,10] the use of potassium aryl trifluoroborates, potassium trihydroxyarylborates or phenyl N-methylimidodiacetic acid (MIDA) arylboronates as alternative arylboronic acid sources.

In a recent effort Van Zeeland and Stanley did show some promising results in achieving efficient construction of sterically congested bisbenzylic and ortho-substituted benzylic quaternary centers (Scheme 7).[34]

![Scheme 7. Pd-catalyzed conjugate additions in an aqueous NaCF$_3$CO$_2$ medium.](image-url)
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Racemic conjugate additions of five ortho-substituted arylboronic acids were performed using aqueous NaCF₃CO₂, at pH 8.2, as the reaction medium. The results generally show considerably higher isolated yields compared to ours and it was postulated that the reactivity of the Pd-catalyst is enhanced by the use of the aqueous NaCF₃CO₂ medium. Additionally, the conditions were also shown to be suitable in the asymmetric variant using Stoltz’ catalytic system.[⁶] Some chiral induction was lost however, as the enantiomeric excess of 71% was somewhat lower than the 93% originally reported by the Stoltz laboratory.

When re-investigation of our developed methodology is aspired, the conditions reported by Van Zeeland and Stanley might serve as a good starting point. The high reaction temperatures needed for construction of the ortho-substituted benzylic quaternary center does raise the question whether it will be useful in the development of an asymmetric variant. High temperatures are generally avoided in asymmetric catalysis as stereochemical induction by the catalyst might erode, although there are exceptions.[³⁵]

5.6 Experimental section

General methods:
All reactions were performed using oven-dried glassware (except the screw cap vials) under an atmosphere of nitrogen (unless otherwise specified) by standard Schlenk techniques, using dry solvents. Reaction temperature refers to the temperature of the oil bath.

Solvents were taken from a MBraun solvent purification system (SPS-800). All other reagents were purchased from Sigma-Aldrich, Acros, TCI Europe, Combi-Blocks, Strem or Fluorochem and used without further purification unless noted otherwise. Silver hexafluoroantimonate (AgSbF₆), silver hexafluorophosphate (AgPF₆), and silver trifluoroacetate (AgCF₃CO₂) were stored in a nitrogen dry-box in the absence of light. The bisoxazoline ligand used was stored at -20 °C. PdCl₂-(R,R-PhBOX) catalyst was prepared as described and stored in the fridge at 4 °C.

TLC analysis was performed on Merck silica gel 60/Kieselguhr F254, 0.25 mm. Compounds were visualized using either Seebach’s stain (a mixture of phosphomolybdic acid (25 g), cerium (IV) sulfate (7.5 g), H₂O (500 mL) and H₂SO₄ (25 mL)), a KMnO₄ stain (K₂CO₃ (40 g), KMnO₄ (6 g), H₂O (600 mL) and 10% NaOH (5 mL)), an Alizarin stain[³⁶] or elemental iodine.

Flash chromatography was performed using Silicycle silica gel type SiliaFlash P60 (230 – 400 mesh) as obtained from Screening Devices or with automated column chromatography using a Reveleris flash purification system purchased from Grace Davison Discovery Sciences.

¹H- and ¹³C-NMR spectra were recorded on a Varian AMX400 or a Varian 400-MR (400 and 101 MHz, respectively) using CDCl₃ or DMSO-d₆ as solvent, unless stated otherwise. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CDCl₃: δ 7.26 for ¹H, δ 77.16 for ¹³C, DMSO-d₆ δ 2.50 for ¹H). Data
are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, td = triple doublet, t = triplet, q = quartet, b = broad, m = multiplet), coupling constants J (Hz), and integration.

GC-MS measurements were performed with an HP 6890 series gas chromatography system equipped with a HP 5973 mass sensitive detector. GC measurements were made using a Shimadzu GC 2014 gas chromatograph system bearing a AT5 column (Grace Alltech) and FID detection.

Enantiomeric excesses were determined by chiral HPLC analysis using a Shimadzu LC-10ADVP HPLC instrument equipped with a Shimadzu SPD-M10AVP diode-array detector. Integration at three different wavelengths (254, 225, 190 nm) was performed and the reported enantiomeric excess is an average of the three integrations. Retention times (t_R) are given in min.

High resolution mass spectra (HRMS) were recorded on a Thermo Scientific LTQ Orbitrap XL. Optical rotations were measured on a Schmidt+Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/mL) at ambient temperature (±20 °C).

General procedure for the racemic conjugate additions:
To a 4 mL vial with Teflon-coated screw cap was added 2,2'-bipyridine (0.05 mmol, 7.5 mol%) and palladium trifluoroacetate (0.033 mmol, 5 mol%). The solids were dissolved in a pre-mixed MeOH/H_2O (9:1) solution (2 mL) and the vial was placed in a pre-heated oil bath at 60 °C and stirred for 15 min. The solution was cooled to rt and the α,β-unsaturated ketone (3.33 mmol, 5 eq) and the boronic acid (0.66 mmol, 1 eq), dissolved in a solution of MeOH/H_2O (9:1, 1 mL) were added. The reaction was stirred at 60 °C for 48 h. The crude mixture was flushed over a short silica plug and the elute was dried over MgSO_4, filtered and concentrated under reduced pressure. Then the mixture was purified by flash chromatography with pentane : ether as the eluent.

PdCl_2-(R,R-PhBOX) catalyst:
To an oven-dried Schlenk flask charged with palladium(II) chloride (520 mg, 2.93 mmol) was added a solution of (4R,4'R)-2,2'-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole) (1.00 g, 2.99 mmol, 1.02 eq) in dry MeCN (15 mL). An additional 10 mL of dry MeCN was used to rinse the walls of the flask. The Schlenk flask was equipped with a reflux condenser and the reaction was refluxed for 3.5 h. Over time an orange-red suspension formed which after the reaction was cooled to 0 °C with an ice-bath and filtered through a glass-filter (pore-size 4). The residue was washed twice with pentane and dried under an N_2 atmosphere. PdCl_2-(R,R-BOX) catalyst (1.22 g, 2.38 mmol, 81% yield) was isolated as an orange solid.

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$^1$H-NMR (400 MHz, DMSO-$d_6$): $d = 7.54$–$7.40$ (m, 10H), 5.81 ($d, J = 8.6$ Hz, 2H), 4.96 ($t, J = 9.1$ Hz, 2H), 4.55 ($d, J = 8.2$ Hz, 2H), 1.96 ppm (s, 6H).

Characterization matched the previously reported data.$^7$

General Procedure for the enantioselective conjugate additions:
A 4 mL vial with Teflon-coated screw-cap was charged with Pd-Catalyst (0.021 mmol, 4 mol%), the ortho-substituted arylboronic acid (0.052 mmol, 10 mol%), and ammonium hexafluorophosphate (0.052 mmol, 10 mol%). To the solids was added dichloroethane (0.75 mL) and the mixture was stirred at rt for 5 min. Not all solids dissolved. To the reaction mixture was subsequently added the $\beta,\beta$-disubstituted enone (3.64 mmol, 7 eq) in dichloroethane (0.75 mL). Deionized water (4.16 mmol, 8 eq) was added. The vial was sealed and placed in a pre-heated oil bath at 60 °C. Within 30 min a black precipitate (AgCl) was formed. The reaction was allowed to stir for 48 h. The reaction mixture was cooled to rt where after it was filtered through a small silica plug, and flushed with ether (2-3 column volumes). The eluate was concentrated under reduced pressure and the resulting oil was purified using flash chromatography employing a mixture of pentane : ether as the eluent.

General procedure for the preparation of Raney nickel:
An aqueous solution of NaOH (6.4 M, 500 mL) was cooled with an ice/salt bath. To the cooled solution a nickel/aluminum alloy (Ni : Al = 50 : 50, 100 g) was added in small portions over two h. The temperature was never allowed to rise above 15 °C. After addition, the ice/salt bath was removed and the suspension was allowed to warm to rt. The water was decanted and an aqueous solution of NaOH (2.5 M, 200 mL) was added to the residue. Stirring was applied for 15 min where after the suspension was allowed to settle. Decantation of the alkali solution was performed and the residue was washed with water. Washing and decantation was repeated until the washings were pH-neutral. The Raney nickel residue was washed with three portions of EtOH (95%, 600 mL) and three times with absolute EtOH (600 mL). The Raney Nickel was stored under absolute ethanol.

Important notes for the preparation and use of Raney nickel:
- During preparation of the Raney nickel significant quantities of hydrogen gas evolved
- The Raney nickel as prepared contains adsorbed hydrogen (sponge catalyst) and is therefore highly flammable!
- Raney nickel is pyrophoric when dry!
- Storage of the Raney Nickel can lead to pressure build-up in the storage container!
(S)-3-(2,3-dimethoxy-5-methylphenyl)-3-methylcyclopentanone (3g):
An oven-dried Schlenk tube was charged with PdCl₂-(R,R-PhBOX) (83 mg, 0.163 mmol, 8 mol%), (2,3-dimethoxy-5-methylphenyl)boronic acid 2g (800 mg, 4.08 mmol, 1 eq), silver trifluoroacetate (90 mg, 0.408 mmol, 20 mol%), and ammonium hexafluorophosphate (66.5 mg, 0.408 mmol, 20 mol%). Three vacuum-nitrogen cycles were applied. To the solids was added dichloroethane (4 mL) and the mixture was stirred at rt for 5 min. Not all solids dissolved. To the mixture was added 3-methylcyclopent-2-enone (2.8 ml, 28.5 mmol, 7 eq) in dichloroethane (4 mL). Demineralized water (8 eq) was added. The Schlenk tube was sealed and the reaction was heated to 60 °C in a pre-heated oil bath. Within 30 min the precipitate (Ag-salt) turned black. The reaction was allowed to react for 48 h.

The reaction mixture was cooled to rt where after it was filtered through a small silica plug, an flushed with ether (2-3 column volumes). The elute was concentrated under reduced pressure and the resulting oil was purified using flash column chromatography employing a mixture of pentane : ether (5 : 1) as the eluent. (S)-3-(2,3-dimethoxy-5-methylphenyl)-3-methylcyclopentanone (367 mg, 36% yield, 92% ee) 3g was isolated as a colorless oil which solidified overnight.

$^1$H-NMR (400 MHz, CDCl₃) δ 6.67 (d, J = 1.7, 1H), 6.60 (d, J = 1.3, 1H), 3.85 (s, 3H), 2.66 (dd, J = 63.9, 10.0, 2H), 2.44 – 2.25 (m, 4H), 2.31 (s, 3H), 1.36 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl₃) δ 219.30, 152.77, 145.17, 141.03, 132.79, 118.69, 111.80, 60.26, 55.52, 52.56, 42.77, 36.00, 35.16, 27.01, 21.38.


Chiral HPLC analysis on a Chiracel AD-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 15.1 (minor) and 16.0 (major)

[$\alpha$]$_D^{20}$ = -47.2 (CHCl₃, c = 0.0041) for a 92% ee sample.

Melting point = 76.2 °C
**Pd-catalyzed Asymmetric Conjugate Addition of Ortho-substituted Arylboronic Acids**


\[
\begin{array}{c}
\text{Pd} \left( \text{CF}_3 \text{CO}_2 \right)_2 \text{ (40 mol\%)} \\
\text{Ligand L1} \text{ (40 mol\%)} \\
\text{O}_2 \text{ (1 atm.)} \\
\text{DMSO, 80 °C, 24 h} \\
\text{79\%} \\
\end{array}
\]

(R)-4-(2,3-dimethoxy-5-methylphenyl)-4-methylcyclopent-2-enone (5):  
This reaction was performed, based on the procedure by Stahl *et al.*[26] To an oven-dried Schlenk tube were added palladium trifluoroacetate (82 mg, 0.248 mmol, 40 mol%), and 5H-cyclopenta[1,2-b:5,4-b']dipyridin-5-one L1 (45.1 mg, 0.248 mmol, 40 mol%). To the mixture was added a solution of (S)-3-(2,3-dimethoxy-5-methylphenyl)-3-methylcyclopentanone 3g (150 mg, 0.604 mmol) in DMSO (2 mL). An oxygen filled balloon (1 atm) was attached to the reaction set up. While vigorously stirring, the Schlenk tube was purged with three vacuum/O\_2 cycles. The reaction mixture was allowed to stir at 80 °C for 24 h. GC-MS showed complete conversion of the starting material. The reaction was cooled to rt and diluted with water. The aqueous layer was extracted five times with CH\_2Cl\_2 and the combined organic layers were dried over Na\_2SO\_4, filtered and concentrated under reduced pressure. Flash column chromatography employing pentane : ether (3:2) furnished pure (R)-4-(2,3-dimethoxy-5-methylphenyl)-4-methylcyclopent-2-enone (117 mg, 79% yield) 5 as a colorless oil, which solidified overnight.

\[^1\text{H}-\text{NMR} \text{ (400 MHz, CDCl}_3\text{) } \delta 7.84 \text{ (d, } J = 5.6, \text{ 1H)}, 6.66 \text{ (d, } J = 1.6, \text{ 1H)}, 6.57 \text{ (d, } J = 1.3, \text{ 1H)}, 6.13 \text{ (d, } J = 5.6, \text{ 1H)}, 3.82 \text{ (s, 3H)}, 3.76 \text{ (s, 3H)}, 2.64 \text{ (dd, } J = 49.8, 18.6, \text{ 2H)}, 2.28 \text{ (s, 3H)}, 1.55 \text{ (s, 3H)}\]

\[^{13}\text{C}-\text{NMR} \text{ (101 MHz, CDCl}_3\text{) } \delta 209.78, 171.37, 152.96, 145.14, 137.98, 132.96, 130.55, 119.17, 112.45, 60.45, 55.71, 51.07, 47.33, 28.26, 21.44.\]

HRMS (ESI\(^+\)): Calculated mass [M+H]\(^+\) C\(_{15}\)H\(_{19}\)O\(_3\) = 247.13287; found: 247.13301  
(ESI\(^+\)): Calculated mass [M+Na]\(^+\) C\(_{15}\)H\(_{19}\)O\(_3\)Na = 269.1148; found: 269.1150.  
\([\alpha]\)\(_D\)\(^{30}\) = -31.2 (CHCl\(_3\), c = 0.006) for a 92% ee sample.
(R)-4-(2,3-dimethoxy-5-methylphenyl)-4,5,5-trimethylcyclopent-2-enone (6):
The dimethylation was based on a procedure by Srikrishna et al. [27] To a suspension of NaH (341 mg, 60% dispersion in oil, 8.53 mmol, washed with pentane, 15 eq) in dry THF (4 mL) was added a solution of (R)-4-(2,3-dimethoxy-5-methylphenyl)-4-methylcyclopent-2-enone (140 mg, 0.568 mmol) 5 in dry THF (3 mL) and DMF (0.35 mL). The resulting suspension was stirred for 15 min where after iodomethane (708 μL, 11.4 mmol, 20 eq) was added. The reaction was stirred for 7 h after which GC-MS and TLC indicated complete conversion of the starting material. The reaction was carefully quenched with water (5 mL) where after the phases were separated. The aqueous phase was extracted with ether (3x5 mL) and the combined organic layers were treated once with brine. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography employing pentane : ether (4 : 1) afforded (R)-4-(2,3-dimethoxy-5-methylphenyl)-4,5,5-trimethylcyclopent-2-enone (120 mg, 77% yield) 6 as a colorless oil. The oil crystallized quickly giving transparent (white appearing!) crystals.

1H-NMR (400 MHz, CDCl₃) δ 7.93 (d, J = 5.6, 1H), 6.66 (d, J = 1.7, 1H), 6.49 (s, 1H), 6.07 (d, J = 5.8, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 2.30 (s, 3H), 1.48 (s, 3H), 1.25 (s, 3H), 0.66 (s, 3H).

13C-NMR (101 MHz, CDCl₃) δ 214.55, 171.22, 152.68, 145.27, 135.91, 132.72, 125.63, 120.57, 112.05, 60.24, 55.53, 50.80, 26.00, 22.20, 21.34, 19.62, 13.95.


[α]D²⁰ = -58.5 (CHCl₃, c = 0.004) for a 92% ee sample.
(S)-1,2-dimethoxy-5-methyl-3-(1,2,2-trimethylcyclopentyl)benzene (7): The procedure was based on a publication by Myers.\textsuperscript{[21a]} To a solution of \((R)-4-(2,3\text{-dimethoxy-5-methylphenyl})-4,5,5\text{-trimethyl cyclopent-2-enone (100 mg, 0.364 mmol) 6 in dry toluene (5 mL) was added Lawesson’s reagent (177 mg, 0.437 mmol, 1.2 eq). The suspension was heated to reflux for 45 min. The suspension turned into a clear bright pink solution over time. TLC using pentane : ether (4 : 1) indicated complete conversion of the enone into the thioenone. The reaction mixture was cooled to rt, filtered over a small fluorosil column and flushed with CH\(_2\)Cl\(_2\). The elute was concentrated under reduced pressure and purified using flash column chromatography (5\% EtOAc in hexane) only isolating the pink fractions. The fractions were concentrated to a bright pink oil which was dissolved in EtOH (8 mL). To the solution freshly prepared Raney nickel was added. A hydrogen balloon was fixed to the flask and the reaction mixture was purged with three vacuum/H\(_2\) cycles. The reaction was stirred overnight where after the reaction was filtered over a silica plug and flushed with pentane : ether (1 : 1). Evaporation of the solvent under reduced pressure gave a slight yellow oil. Flash chromatography using 4\% ether in pentane afforded (S)-1,2-dimethoxy-5-methyl-3-(1,2,2-trimethyl cyclopentyl)benzene (62 mg, 0.236 mmol, 65\% yield) 7 as a colorless oil. The oil crystallized overnight producing transparent (white appearing!) crystals.

\[ \text{H-NMR (400 MHz, CDCl}_3\text{)} \delta 6.82 (s, 1H), 6.67 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.76 – 2.63 (m, 1H), 2.36 (s, 3H), 1.92 – 1.74 (m, 3H), 1.74 – 1.64 (m, 1H), 1.63 – 1.51 (m, 1H), 1.43 (s, 3H), 1.20 (s, 3H), 0.78 (s, 3H). \]

\[ \text{C-NMR (101 MHz, CDCl}_3\text{)} 153.10, 146.76, 140.17, 131.60, 121.69, 111.11, 60.39, 55.64, 51.62, 45.03, 40.98, 39.02, 26.92, 25.30, 24.25, 21.76, 20.44. \]

HRMS (ESI+): Calculated mass \([M+H]^+ C_{17}H_{27}O_2^+ = 263.2005\); found: 263.2007.

\([\alpha]_D^{20} = -26.1 (\text{CHCl}_3, c = 0.00115)\) for a 92\% ee sample.
(S)-5-methyl-3-(1,2,2-trimethylcyclopentyl)benzene-1,2-diol (herbertenediol):  
The procedure was based on a publication by Myers.[21a] To a solution of (S)-1,2-dimethoxy-5-methyl-3-(1,2,2-trimethylcyclopentyl)benzene (15 mg, 0.057 mmol, 1 eq) 7 in dry CH₂Cl₂ (1 mL) at 0 °C was added BBr₃ (285 μL, 0.285 mmol, 5 eq, 1 M in CH₂Cl₂). The reaction mixture was allowed to warm to rt and was stirred for 1 h. TLC using 5% ether in pentane indicated complete conversion of the starting material. The reaction mixture was added to a 2% aqueous solution of NaHCO₃. The phases were separated and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure affording a white solid. Flash column chromatography using pentane : ether (7 : 3) afforded (S)-5-methyl-3-(1,2,2-trimethylcyclopentyl)benzene-1,2-diol (11 mg, 0.047 mmol, 82 % yield) I as a white solid.

1H-NMR (400 MHz, CDCl₃) δ 6.69 (s, 1H), 6.58 – 6.54 (m, 1H), 5.35 (s, 1H), 4.98 (s, 1H), 2.68 – 2.54 (m, 1H), 2.23 (s, 3H), 1.82 – 1.70 (m, 3H), 1.70 – 1.62 (m, 1H), 1.61 – 1.50 (m, 0H), 1.42 (s, 3H), 1.19 (s, 3H), 0.77 (s, 3H).

13C-NMR (101 MHz, CDCl₃) δ 143.48, 141.03, 133.63, 128.48, 122.06, 113.58, 51.26, 44.99, 41.08, 39.37, 26.98, 25.56, 22.98, 21.30, 20.41.

HRMS (ESI-) Calculated mass [M-H]⁻ C₁₅H₂₁O₂⁻ = 233.1536; found: 233.1544.

[α]D²⁰ = -52.3 (CHCl₃, c = 0.0047) for a 92% ee sample.

The analytical data matches with that of the natural isolate.[18]
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(5S)-3-(2,5-dimethoxy-4-methylphenyl)-3-methylcyclopentanone (3j):
To an oven dried Schlenk tube were added palladium catalyst (42 mg, 0.143 mmol, 8 mol%), (2,5-dimethoxy-4-methylphenyl)boronic acid (350 mg, 1.79 mmol) 2j, silver trifluoroacetate (44 mg, 0.358 mmol, 20 mol%) and ammonium hexafluorophosphate (32 mg, 0.358 mmol, 20 mol%) and the Schlenk tube was alternated through three vacuum/nitrogen cycles. Dichloroethane (2.5 mL) was added to the solids and the mixture was stirred for 10 min at rt. Not all the solids dissolved. Then, 3-methyl cyclopent-2-enone (1.2 g, 12.5 mmol, 7 eq) in dichloroethane (2.5 mL) was added. Demineralized water (260 μL, 14.3 mmol, 8 eq) was added and the reaction was stirred at 60 °C. After 48 h, the mixture was cooled to rt, filtered over a silica plug and flushed with ether. The elute was concentrated and purified by flash column chromatography using pentane : ether (4 : 1). (5S)-3-(2,5-dimethoxy-4-methylphenyl)-3-methylcyclopentanone 3j was obtained as a colorless oil (93 mg, 21% yield, 74% ee).

1H-NMR (400 MHz, CDCl₃) δ 6.71 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.63 (dd, J = 18.1, 6.5, 2H), 2.44 – 2.26 (m, 4H), 2.21 (s, 3H), 1.38 (s, 3H).

13C-NMR (101 MHz, CDCl₃) δ 219.63, 151.34, 151.33, 134.04, 125.33, 114.67, 109.75, 56.16, 55.53, 52.35, 42.58, 36.33, 34.94, 26.28, 15.87.


[α]D²⁰ = -15.6 (CHCl₃, c = 0.002) for a 74% ee sample.

Chiral HPLC analysis on a Chiracel AD-H column, n-Heptane : i-PrOH = 97 : 3, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 15.0 (minor) and 16.0 (major).

(R)-4-(2,5-dimethoxy-4-methylphenyl)-4-methylcyclopent-2-enone (8):
This reaction was performed based on the procedure by Stahl et al.\textsuperscript{[26]} To an oven-dried Schlenk tube was added palladium trifluoroacetate (150 mg, 0.47 mmol, 50 mol%) and diazfluorenone (85 mg, 0.47 mmol, 50 mol%). Compound 3j (293 mg, 1.18 mmol) was dissolved in DMSO (4 mL) and added to the mixture. The Schlenk was purged with three vacuum/oxygen cycles, and the reaction was allowed to stir for 24 h at rt. Water (12 mL) was added and the reaction mixture was extracted with DCM (3x30 mL). The combined organic layers were washed with brine (30 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography with pentane : ether (4 : 1) to yield (R)-4-(2,5-dimethoxy-4-methylphenyl)-4-methylcyclopent-2-enone 8 as a colorless oil (157 mg, 54% yield).

\[^1H\text{-NMR}\text{ (400 MHz, CDCl}_3\text{)} \delta 7.80 \text{ (d, } J = 5.7, 1\text{H}), 6.71 \text{ (s, 1\text{H}), 6.66 \text{ (s, 1\text{H}), 6.16 \text{ (d, } J = 5.6, 1\text{H}), 3.79 \text{ (s, 3\text{H}), 3.75 \text{ (s, 3\text{H}), 2.67 \text{ (dd, } J = 83.9, 18.7, 2\text{H}), 2.21 \text{ (s, 3\text{H}), 1.57 \text{ (s, 3\text{H).}}}}]

\[^{13}C\text{-NMR}\text{ (101 MHz, CDCl}_3\text{)} \delta 210.02, 170.73, 151.23, 151.17, 131.15, 130.88, 126.02, 114.83, 110.00, 56.21, 55.60, 50.36, 47.13, 27.36, 15.98.

HRMS (ESI\textsuperscript{+}): Calculated mass [M+H]\textsuperscript{+} C$_{15}$H$_{19}$O$_3$\textsuperscript{+} = 247.13287; found: 247.13284.

(ESI\textsuperscript{+}): Calculated mass [M+Na]\textsuperscript{+} C$_{15}$H$_{18}$O$_3$Na\textsuperscript{+} = 269.1148; found: 269.1148.

\[^{[\alpha]}D^{20} = -55.2 \text{ (CHCl}_3, c = 0.006) \text{ for a 74\% ee sample.}}]

(R)-4-(2,5-dimethoxy-4-methylphenyl)-4,5,5-trimethylcyclopent-2-enone (9):
The dimethylation was based on a procedure by Srikrishna et al.\textsuperscript{[27]} NaH (222 mg, 5.55 mmol, 15 eq, 60% suspension in oil) was washed with pentane and suspended in dry THF (3 mL). Compound 8 (92 mg, 0.37 mmol) was added in dry THF (2 mL) and dry DMF (0.23 mL) and stirred for 15 min. MeI (0.46 mL, 7.4 mmol, 20 eq) was added and the reaction was stirred at rt. After 7 h, the reaction was carefully quenched with H$_2$O (5
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mL) at 0 °C and extracted with ether (3x10 mL). The combined organic layers were washed with brine (10 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography with pentane : ether (4 : 1) to yield 9 as a colorless oil (64 mg, 62% yield).

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.88 (d, $J = 5.9$, 1H), 6.71 (s, 1H), 6.53 (s, 1H), 6.12 (d, $J = 5.7$, 1H), 3.77 (s, 6H), 2.21 (s, 3H), 1.49 (s, 3H), 1.26 (s, 3H), 0.67 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 214.85, 170.68, 151.56, 151.36, 129.60, 126.68, 125.78, 114.59, 111.27, 56.09, 55.30, 54.73, 50.78, 25.65, 24.89, 19.99, 15.97.

HRMS (ESI+): Calculated mass [M+H]$^+$ C$_{17}$H$_{23}$O$_3$ = 275.1641; found: 275.1641.

ESI+): Calculated mass [M+Na]$^+$ C$_{17}$H$_{22}$O$_3$Na$^+$ = 297.1461; found: 297.1461.

(R)-3-(2,5-dimethoxy-4-methylphenyl)-2,2,3-trimethylcyclopentanone (10)

Pd/C (20 mg, 10% activated Pd on charcoal) was added to an oven-dried Schlenk tube. Compound 9 (47 mg, 0.17 mmol) was dissolved in ethanol (1 mL) and added to the tube, which was subsequently equipped with a hydrogen balloon and subjected to three vacuum/hydrogen cycles. After stirring for 3.5 h at rt, the mixture was flushed over a silica plug and concentrated under reduced pressure to give 10 as a colorless oil (45 mg, 96% yield).

$^1$H-NMR (400 MHz, CDCl$_3$) δ 6.85 (s, 1H), 6.68 (s, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 2.49 (ddd, $J = 20.2$, 17.1, 10.2, 3H), 2.21 (s, 3H), 2.10 – 1.98 (m, 1H), 1.38 (s, 3H), 1.23 (s, 3H), 0.70 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 222.80, 151.85, 151.23, 132.44, 125.25, 114.29, 111.47, 56.19, 54.76, 52.67, 48.24, 34.72, 32.56, 23.47, 21.74, 21.57, 15.76.

HRMS (ESI+): Calculated mass [M+H]$^+$ C$_{17}$H$_{25}$O$_3$ = 277.1798; found: 277.1798.

[$\alpha$]$_D^{20}$ = -13.2 (CHCl$_3$, $c = 0.005$) for a 75% ee sample.
(S)-2-methyl-5-(1,2,2-trimethyl-3-oxocyclopentyl)cyclohexa-2,5-diene-1,4-dione (enokipodin B)

This reaction was performed according to the procedure of Srikrishna et al.\[37\] 10 (44 mg, 0.16 mmol) was dissolved in CH$_3$CN (3 mL) and water (3 mL) and added to an oven-dried Schlenk tube. CAN (219 mg, 0.4 mmol, 2.5 eq) was added and the reaction was stirred at rt for 1 h. The reaction mixture was extracted with DCM (3x5 mL) and the combined organic layers were washed with brine (10 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The purification was performed using flash chromatography with pentane : ether (4 : 1) to yield enokipodin B as a yellow solid (33 mg, 84% yield).

$^1$H-NMR (400 MHz, CDCl$_3$) δ 6.69 (s, 1H), 6.56 (s, 1H), 2.54 – 2.35 (m, 2H), 2.27 (dd, J = 21.7, 10.9, 1H), 2.04 (s, 3H), 1.91 – 1.83 (m, 1H), 1.32 (s, 3H), 1.22 (s, 3H), 0.76 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 221.00, 188.30, 187.89, 153.58, 144.57, 135.42, 134.25, 52.47, 49.07, 33.88, 31.19, 23.21, 22.27, 20.75, 15.04.

HRMS (ESI+): Calculated mass [M+H]$^+$ C$_{15}$H$_{19}$O$_3$ = 247.1328; found: 247.1328.

$[\alpha]_D^{20}$ = -24.8 (CHCl$_3$, c = 0.01) for a 74% ee sample.

(2R,5R)-5,8,10-tetramethyl-2,3,4,5-tetrahydro-2,5-methanobenzo[b]oxepine-2,7-diol (ent-enokipodin A):

Compound 10 (50 mg, 0.18 mmol), was dissolved in DCM (10 mL) and cooled to 0 °C. BBr$_3$ (0.9 mL, 0.9 mmol, 5 eq) was added dropwise. The light brown solution was stirred for 24 h at rt. The reaction was quenched with a saturated aqueous solution of NaHCO$_3$ (10 mL) and extracted with DCM (3x10 mL). The combined organic layers were washed with brine (10 mL), dried over Na$_2$SO$_4$, filtered and concentrated. The
crude mixture was purified by flash chromatography with pentane : ether (3 : 1) to yield pure enokipodin A as transparent (white appearing) clear crystals (25 mg, 57% yield).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 6.55 (s, 1H), 6.50 (s, 1H), 4.25 (s, 1H), 2.69 (s, 1H), 2.17 (s, 3H), 2.14 – 2.03 (m, 2H), 1.90 (td, $J = 12.1, 6.5$, 1H), 1.82 – 1.73 (m, 1H), 1.24 (s, 3H), 1.09 (s, 3H), 0.80 (s, 3H).

$^{13}$C-NMR (101 MHz, DMSO-$d_{6}$) $\delta$ 148.34, 145.05, 130.24, 122.06, 115.91, 110.41, 109.01, 46.73, 42.82, 38.34, 35.20, 18.44, 15.96, 15.79, 15.64.

HRMS (APCI+): Calculated mass [M+H]$^+$ C$_{15}$H$_{21}$O$_3$ $^+$ = 249.1485; found: 249.1482.

$[\alpha]_D^{20} = +77.0$ (CHCl$_3$, $c = 0.006$) for a 74% ee sample.

3-methyl-3-(o-tolyl)cyclopentenone (3a):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 82% yield, enantioselective synthesis 23% yield, 90% ee.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.25 – 7.12 (m, 4H), 2.67 (dd, $J = 55.6, 17.5$, 2H), 2.45 (s, 3H), 2.53 – 2.35 (m, 4H), 1.38 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 218.32, 146.40, 135.37, 132.40, 126.34, 126.07, 125.92, 52.72, 44.31, 35.85, 35.77, 26.40, 22.44.

HRMS (ESI+): Calculated mass [M+Na]$^+$ C$_{13}$H$_{16}$ONa$^+$ = 211.1093; found: 211.1084.

$[\alpha]_D^{20} = -35.9$ (CHCl$_3$, $c = 0.01$) for a 90% ee sample.

Chiral HPLC analysis on a Chiracel OB-H column, n-Heptane : i-PrOH = 99 : 1, 40 ºC, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 25.8 (minor) and 28.5 (major).

Chiral HPLC analysis on a Chiracel AS-H column, n-Heptane : i-PrOH = 99 : 1, 40 ºC, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 13.0 (minor) and 14.0 (major).
CHAPTER 5

Chiral HPLC analysis Phenomenex LUX 5μ Cellulose-3 column, \( n \)-Heptane : \( i \)-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 9.5 (minor) and 10.5 (major).

\[
\begin{align*}
3-(2\text{-methoxyphenyl})-3\text{-methylcyclopentanone (3b)}: \\
\text{This compound was prepared according to the general procedure and purified employing flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 69% yield, enantioselective synthesis 45% yield, 80% ee.}
\end{align*}
\]

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \( \delta 7.26 - 7.10 \) (m, 2H), \( 6.95 - 6.82 \) (m, 2H), \( 3.79 \) (s, 3H), 2.59 (dd, \( J = 18.1, 18.1 \)) 2H), 2.41 - 2.23 (m, 4H), 1.36 (s, 3H).

\(^{13}\)C-NMR (101 MHz, CDCl\(_3\)) \( \delta 219.93, 157.66, 136.14, 127.72, 126.29, 120.52, 111.39, 54.97, 52.31, 42.66, 36.41, 34.90, 26.21.

HRMS (ESI+): Calculated mass \([M+H]^+\) \( C_{13}H_{17}O_2 \) = 205.1223; found: 205.1214.

\([\alpha]_D^{20} = -21.0 \) (CHCl\(_3\), \( c = 0.01 \)) for a 80% ee sample.

Chiral HPLC analysis on a Chiracel AD-H column, \( n \)-Heptane : \( i \)-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 19.0 (minor) and 20.9 (major).

Chiral HPLC analysis on a Phenomenex LUX 5μ Cellulose-3 column, \( n \)-Heptane : \( i \)-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 9.8 (minor) and 11.5 (major).

Chiral HPLC analysis on a Chiracel OB-H column, \( n \)-Heptane : \( i \)-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 24.8 (minor) and 29.3 (major).
Pd-catalyzed Asymmetric Conjugate Addition of Ortho-substituted Arylboronic Acids

3-(2-fluorophenyl)-3-methylcyclopentanone (3c):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 20% yield (51% with double catalyst loading), enantioselective synthesis 20% yield, 95% ee.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.32 – 7.23 (m, 2H), 7.19 – 7.03 (m, 2H), 2.71 – 2.59 (m, 2H), 2.54 – 2.34 (m, 4H), 1.44 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 218.50, 218.48, 162.57, 160.11, 134.99, 134.87, 128.45, 128.37, 127.11, 127.05, 124.28, 124.25, 116.62, 116.39, 52.09, 52.06, 42.29, 42.27, 36.26, 36.25, 34.81, 34.78, 26.96, 26.94 (Spectrum contains the double amount of peaks due to carbon-fluorine coupling).

HRMS (ESI+): Calculated mass [M+H]$^+$ C$_{12}$H$_{14}$OF$^+$ = 193.1023; found: 193.1014.

$[^\alpha]_D^{20} = -23.8$ (CHCl$_3$, c = 0.01) for a 95% ee sample.

Chiral HPLC analysis on a Chiracel AD-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 20.4 (major) and 21.7 (minor).

Chiral HPLC analysis on a Chiracel AS-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 12.1 (major) and 13.2 (minor).
3-(2-chlorophenyl)-3-methylcyclopentanone (3d):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 12% yield (31% with double catalyst loading), enantioselective synthesis 8% yield (12% with double catalyst loading), 94% ee.

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.38 (dd, $J = 7.8, 1.5, 1$H), 7.32 (dd, $J = 7.8, 1.8, 1$H), 7.25 (td, $J = 7.6, 1.6, 1$H), 7.18 (td, $J = 7.6, 1.7, 1$H), 2.78 (dd, $J = 101.0, 17.9, 2$H), 2.55 – 2.34 (m, 4H), 1.48 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 218.51, 144.94, 133.48, 131.83, 128.02, 127.73, 127.12, 52.23, 44.49, 36.28, 35.22, 25.68.

HRMS (ESI+): Calculated mass [M+H]$^+$ C$_{12}$H$_{14}$OCl$^+$ = 209.07277; found: 209.07185 (ESI+): Calculated mass [M+Na]$^+$ C$_{12}$H$_{13}$OClNa$^+$ = 231.0547; found: 231.0537.

$[^{[\alpha]}]_D^{20} = -22.4$ (CHCl$_3$, c = 0.01) for a 94% ee sample.

Chiral HPLC analysis on a Chiracel OD-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 23.9 (minor) and 29.2 (major).

Chiral HPLC analysis on a Phenomenex LUX 5μ Cellulose-3 column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 1.0 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 9.5 (major) and 10.4 (minor).

3-(dibenzo[b,d]furan-4-yl)-3-methylcyclopentanone (3e)
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 69% yield, enantioselective synthesis 51% yield, 93% ee.
Pd-catalyzed Asymmetric Conjugate Addition of Ortho-substituted Arylboronic Acids

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.91 (d, $J = 7.7$, 1H), 7.82 (dd, $J = 6.1$, 2.8, 1H), 7.56 (d, $J = 8.2$, 1H), 7.47 – 7.40 (m, 1H), 7.34 – 7.29 (m, 1H), 7.27 (d, $J = 3.6$, 2H), 2.83 (dd, $J = 49.5$, 17.8, 2H), 2.60 – 2.30 (m, 4H), 1.56 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 218.76, 155.77, 153.87, 132.25, 127.22, 124.85, 124.06, 123.75, 122.92, 122.80, 120.65, 119.19, 111.70, 51.94, 42.56, 36.48, 34.74, 26.77.

HRMS (ESI+): Calculated mass [M+H]$^+$ C$_{18}$H$_{17}$O$_2$$^+$ = 265.1223; found: 265.1212.

$[\alpha]_{D}^{20} = -15.8$ (CHCl$_3$, $c = 0.01$) for a 93% ee sample.

Chiral HPLC analysis on a Chiracel AD-H column, $n$-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 25.9 (major) and 29.5 (minor).

Chiral HPLC analysis on a Chiracel OD-H column, $n$-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 37.0 (major) and 44.3 (minor).

Chiral HPLC analysis on a Phenomenex LUX 5$\mu$ Cellulose-3 column, $n$-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 1.0 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 16.7 (minor) and 23.8 (major).

3-methyl-3-(naphthalen-1-yl)cyclopentenone (3f):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 73% yield, enantioselective synthesis 20% yield (38% with double catalyst loading), 85% ee.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 8.20 (d, $J = 8.1$, 1H), 7.93 – 7.86 (m, 1H), 7.82 – 7.72 (m, 1H), 7.54 – 7.45 (m, 2H), 7.45 – 7.39 (m, 2H), 2.89 (dd, $J = 18.1$, 7.6, 2H), 2.72 – 2.34 (m, 4H), 1.70 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 218.50, 143.75, 135.07, 131.22, 129.78, 128.11, 125.79, 125.43, 125.30, 125.21, 123.46, 53.90, 44.62, 36.67, 36.38, 27.91.

HRMS (ESI+): Calculated mass [M+H]$^+$ C$_{16}$H$_{17}$O$^+$ = 225.1273; found: 225.1264.
[\alpha]_D^{20} = -23.2 (CHCl_3, c = 0.01) for a 85% ee sample.

Chiral HPLC analysis on a Chiracel AS-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 1.0 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 24.4 (major) and 27.5 (minor).

Chiral HPLC analysis on a Phenomenex LUX 5\mu Cellulose-3 column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 1.0 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times for racemate (min): 19.8 and 37.3.

3-(2,3-dimethoxyphenyl)-3-methylcyclopentanone (3h):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 65% yield, enantioselective synthesis 25% yield, 94% ee.

$^1$H-NMR (400 MHz, CDCl_3) $\delta$ 7.01 (t, $J$ = 8.0, 1H), 6.84 (dd, $J$ = 15.7, 7.7, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 2.64 (dd, $J$ = 64.4, 17.9, 2H), 2.45 – 2.26 (m, 4H), 1.37 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl_3) $\delta$ 219.53, 153.22, 147.58, 141.62, 123.44, 118.36, 111.15, 60.41, 55.70, 52.68, 42.96, 36.14, 35.27, 27.11.

HRMS (ESI+): Calculated mass [M+H]$^+$ C_{14}H_{19}O_3$^+$ = 235.1328; found: 235.1327.

[\alpha]_D^{20} = -30.2 (CHCl_3, c = 0.01) for a 94% ee sample.

Chiral HPLC analysis on a Chiracel OD-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 31.3 (minor) and 34.2 (major).
Pd-catalyzed Asymmetric Conjugate Addition of Ortho-substituted Arylboronic Acids

3-(2-methoxy-5-methylphenyl)-3-methylcyclopentanone (3i):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 78% yield, enantioselective synthesis 19% yield (32% with double catalyst loading), 80% ee.

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.05 – 6.98 (m, 2H), 6.80 (d, $J = 8.2$, 1H), 3.80 (s, 3H), 2.62 (dd, $J = 18.2$, 11.5, 2H), 2.47 – 2.31 (m, 4H), 2.30 (s, 3H), 1.38 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 219.92, 155.55, 135.88, 129.46, 127.80, 127.09, 111.37, 55.06, 52.30, 42.53, 36.38, 34.89, 26.23, 20.70.

HRMS (ESI+): Calculated mass [M+H]$^+$ C$_{14}$H$_{19}$O$_2$ $^+$ = 219.13796; found: 219.13786.
(ESI+): Calculated mass [M+Na]$^+$ C$_{14}$H$_{18}$O$_2$Na $^+$ = 241.1199; found: 241.1197.

$[\alpha]_{D}^{20} = -132.3$ (CHCl$_3$, c 0.01) for a 80% ee sample.

Chiral HPLC analysis on a Chiracel AD-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 15.2 (minor) and 16.8 (major).

Chiral HPLC analysis on a Chiracel OD-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 15.9 (major) and 23.8 (minor).

3-(2-methoxy-4-methylphenyl)-3-methylcyclopentanone (3k):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 78% yield, enantioselective synthesis 19% yield (32% with double catalyst loading), 80% ee.
1H-NMR (400 MHz, CDCl₃) δ 7.08 (d, J = 7.8, 1H), 6.74 (d, J = 7.8, 1H), 6.72 (s, 1H), 3.81 (d, J = 4.5, 3H), 2.61 (q, 2H), 2.44 – 2.27 (m, 7H), 1.37 (s, 3H).

13C-NMR (101 MHz, CDCl₃) δ 219.98, 157.51, 137.57, 133.16, 126.10, 120.97, 112.35, 54.89, 52.38, 42.35, 36.40, 34.94, 26.29, 21.22.

HRMS (ESI+): Calculated mass [M+H]^+ C_{14}H_{19}O_{2}^+ = 219.13796; found: 219.13799 (ESI+): Calculated mass [M+Na]^+ C_{14}H_{18}O_{2}Na^+ = 241.11990; found: 241.11995.

[α]D²⁰ = -29.8 (CHCl₃, c = 0.01) for a 80% ee sample.

Chiral HPLC analysis on a Phenomenex LUX 5μ Cellulose-3 column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 1.0 mL/min, UV detection at 190 nm and 225 nm, retention times (min): 35.0 (major) and 37.4 (minor).

Chiral HPLC analysis on a Chiracel AS-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times for racemate (min): 20.7 and 22.6.

Chiral HPLC analysis on a Chiracel OB-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm, and 254 nm, retention times for racemate (min): 35.7 and 39.9.

Chiral HPLC analysis on a Chiracel OD-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times for racemate (min): 32.6 and 37.5.


3-methyl-3-(o-tolyl)cyclohexanone (4a):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 41% yield, enantioselective synthesis 16% yield, 98% ee.
Pd-catalyzed Asymmetric Conjugate Addition of Ortho-substituted Arylboronic Acids

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.25 – 7.21 (m, $J = 4.3$, 1H), 7.17 – 7.10 (m, 3H), 3.00 (d, $J = 14.2$, 1H), 2.54 (s, 3H), 2.47 (d, $J = 14.4$, 2H), 2.31 (t, $J = 6.8$, 2H), 1.99 – 1.82 (m, 2H), 1.67 – 1.57 (m, 1H), 1.42 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 211.86, 144.31, 135.70, 133.49, 127.14, 126.59, 126.24, 55.11, 44.22, 40.84, 36.02, 27.41, 23.43, 21.91.

HRMS (ESI+): Calculated mass [M+H]$^+$ C$_{14}$H$_{19}$O$^+$ = 203.1430; found: 203.1430.

Chiral HPLC analysis on a Chiracel OD-H column, $n$-Heptane : i-PrOH = 99.5 : 0.5, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 23.9 (minor) and 26.9 (major).

3-(2-methoxyphenyl)-3-methylcyclohexanone (4b):
This compound was prepared according to the general procedure and purified with flash column chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 55% yield, enantioselective synthesis 20% yield (42% with double catalyst loading), 96% ee.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.22 (t, $J = 7.6$, 2H), 6.91 (t, $J = 8.1$, 2H), 3.84 (s, 3H), 3.00 (d, $J = 14.1$, 1H), 2.63 – 2.52 (m, 1H), 2.45 (d, $J = 14.9$, 1H), 2.31 (t, $J = 6.9$, 2H), 1.93 – 1.77 (m, 2H), 1.71 – 1.61 (m, 1H), 1.40 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 212.36, 157.84, 134.79, 127.78, 127.40, 120.61, 111.80, 54.92, 53.41, 42.83, 40.97, 35.02, 26.37, 22.18.

HRMS (ESI+): Calculated mass [M+H]$^+$ C$_{14}$H$_{19}$O$^+$ = 219.1379; found: 219.1371.

$[^\alpha]_D^{20} = +52.5$ (CHCl$_3$, $c = 0.01$) for a 96% ee sample.

Chiral HPLC analysis on a Chiracel AD-H column, $n$-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 17.9 (major) and 19.2 (minor).
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Chiral HPLC analysis on a Phenomenex LUX 5μ Cellulose-3 column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 14.0 (minor) and 15.0 (major).

Chiral HPLC analysis on a Chiracel OD-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times for racemate (min): 19.4 and 21.1

3-(2-fluorophenyl)-3-methylcyclohexanone (4c):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 10% yield (with double catalyst loading), enantioselective synthesis 13% yield (23% with double catalyst loading), 95% ee.

\[ \text{HRMS (ESI+): Calculated mass [M+H]$^+$ C}_{13}\text{H}_{16}\text{OF}^+ = 207.1179; \text{found: 207.1170.} \]

\[ [\alpha]_{D}^{20} = +46.1 \text{ (CHCl}_3, c = 0.01) \text{ for a 95% ee sample.} \]

Chiral HPLC analysis on a Phenomenex LUX 5μ Cellulose-3 column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 1.0 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 9.3 (major) and 9.9 (minor).

\[ \text{1H-NMR (400 MHz, CDCl}_3) \delta 7.25 - 7.18 \text{ (m, 2H), 7.10 - 6.98 \text{ (m, 2H), 2.94 (d, } J = 14.7, \text{ 1H), 2.50 - 2.41 \text{ (m, 2H), 2.33 (t, } J = 6.7, \text{ 2H), 1.97 - 1.86 \text{ (m, 2H), 1.68 - 1.58 \text{ (m, 1H), 1.41 (s, 3H).}} \]

\[ \text{13C-NMR (101 MHz, CDCl}_3) \delta 218.55, 218.53, 218.52, 162.59, 160.13, 135.00, 134.88, 128.47, 128.38, 127.12, 127.07, 124.29, 124.26, 116.64, 116.40, 52.11, 52.08, 42.31, 42.28, 36.28, 36.27, 34.83, 34.80, 26.98, 26.96 \text{ (Spectrum contains double amount of peaks due to the carbon-fluorine coupling).} \]

\[ \text{HRMS (ESI+): Calculated mass [M+H]$^+$ C}_{13}\text{H}_{16}\text{OF}^+ = 207.1179; \text{found: 207.1170.} \]

\[ [\alpha]_{D}^{20} = +46.1 \text{ (CHCl}_3, c = 0.01) \text{ for a 95% ee sample.} \]
3-(dibenzo[b,d]furan-4-yl)-3-methylcyclohexanone (4e):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 14% yield (20% with double catalyst loading), enantioselective synthesis 36% yield, 93% ee.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.95 (d, $J = 7.7$, 1H), 7.85 (d, $J = 6.0$, 1H), 7.61 (d, $J = 7.7$, 1H), 7.47 (t, $J = 7.8$, 1H), 7.38 – 7.27 (m, 3H), 3.15 (d, $J = 14.3$, 1H), 2.85 – 2.77 (m, 1H), 2.64 (d, $J = 14.4$, 1H), 2.39 (t, $J = 6.8$, 2H), 2.12 – 1.88 (m, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 211.78, 155.67, 153.77, 131.93, 127.23, 125.10, 124.87, 124.13, 123.08, 122.87, 120.68, 119.38, 111.76, 53.09, 42.75, 41.17, 35.69, 27.06, 22.39.

HRMS (ESI+): Calculated mass [M+H]$^+$ $C_{19}H_{19}O_2^+$ = 279.1379; found: 279.1367

[$\alpha$]$_D^{20}$ = +77.1 (CHCl$_3$, $c = 0.01$) for a 93% ee sample.

Chiral HPLC analysis on a Chiracel OD-H column, n-Heptane : i-PrOH = 99 : 1, 40 ºC, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 25.5 (major) and 27.9 (minor).

Chiral HPLC analysis on a Chiracel AD-H column, n-Heptane : i-PrOH = 99 : 1, 40 ºC, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times for racemate (min): 18.4 and 45.6.

3-methyl-3-(naphthalen-1-yl)cyclohexanone (4f):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 20% yield (34% with double catalyst loading), enantioselective synthesis 26% yield, 95% ee.
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$^1$H-NMR (400 MHz, CDCl$_3$) δ 8.41 (d, $J$ = 8.4, 1H), 7.88 (d, $J$ = 7.5, 1H), 7.74 (dd, $J$ = 6.9, 2.4, 1H), 7.53 – 7.43 (m, 2H), 7.42 – 7.34 (m, 2H), 3.10 (d, $J$ = 13.1, 1H), 2.89 – 2.80 (m, 1H), 2.64 (d, $J$ = 14.6, 1H), 2.36 (t, $J$ = 6.8, 2H), 2.17 (dd, $J$ = 13.6, 9.8, 3.6, 1H), 1.94 – 1.82 (m, 1H), 1.71 (s, 3H), 1.52 – 1.43 (m, 1H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 211.99, 142.28, 135.42, 130.86, 130.05, 128.35, 126.19, 125.31, 125.17, 125.03, 56.15, 44.58, 40.95, 37.23, 28.52, 22.07 (one carbon signal missing due to overlap of two carbon signals).

HRMS (ESI+): Calculated mass [M+H]$^+$ C$_{17}$H$_{19}$O$^+$ = 239.14304; found: 239.14196 (ESI+); Calculated mass [M+Na]$^+$ C$_{17}$H$_{18}$ONa$^+$ = 261.1249; found: 261.1239.

[$\alpha$]$_D^{20}$ = +98.5 (CHCl$_3$, $c$ = 0.01) for a 95% ee sample.

Chiral HPLC analysis on a Phenomenex LUX 5μ Cellulose-3 column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 1.0 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 13.1 (minor) and 15.5 (major).

Chiral HPLC analysis on a Chiracel OD-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times for racemate (min): 27.2 and 41.1.

Chiral HPLC analysis on a Chiracel AD-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times for racemate (min): 18.2 and 26.0.

3-(2,3-dimethoxy-5-methylphenyl)-3-methylcyclohexanone (4g):

This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 44% yield, enantioselective synthesis 19% yield, 94% ee.

$^1$H-NMR (400 MHz, CDCl$_3$) δ 6.66 (s, 1H), 6.61 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.96 (d, $J$ = 14.5, 1H), 2.54 – 2.44 (m, 1H), 2.40 (d, $J$ = 14.3, 1H), 2.34 – 2.30 (m, 2H), 2.28 (s, 3H), 1.92 – 1.80 (m, 2H), 1.71 – 1.58 (m, 2H), 1.39 (s, 3H).
Pd-catalyzed Asymmetric Conjugate Addition of Ortho-substituted Arylboronic Acids

$\text{C-NMR (101 MHz, CDCl}_3) \delta 212.15, 153.13, 145.69, 139.34, 132.86, 120.05, 112.19, 60.38, 55.76, 54.04, 43.10, 40.99, 36.07, 27.61, 22.22, 21.66.$

HRMS (ESI+): Calculated mass $[\text{M+H}]^+$ $C_{16}H_{23}O_3^+ = 263.1641$; found: 263.1642.

(ESI+): Calculated mass $[\text{M+Na}]^+$ $C_{16}H_{22}O_3Na^+ = 285.1461$; found: 285.1462.

$[\alpha]_D^{20} = +29.7$ (CHCl$_3$, c = 0.01) for a 94% ee sample.

Chiral HPLC analysis on a Chiracel AS-H column, $n$-Heptane : $i$-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 18.3 (minor) and 25.5 (major).

Chiral HPLC analysis on a Chiracel AD-H column, $n$-Heptane : $i$-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times for racemate (min): 24.2 and 25.5.


3-(2,3-dimethoxyphenyl)-3-methylcyclohexanone (4h):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 17% yield (28% with double catalyst loading), enantioselective synthesis 44% yield, 99% ee.

$^1\text{H-NMR (400 MHz, CDCl}_3) \delta 6.97 (t, J = 8.1, 1H), 6.85 (d, J = 7.1, 1H), 6.82 (d, J = 8.0, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.97 (d, J = 14.3, 1H), 2.51 (t, J = 9.5, 1H), 2.42 (d, J = 14.4, 1H), 2.35 – 2.25 (m, 2H), 1.94 – 1.80 (m, 2H), 1.71 – 1.58 (m, 1H), 1.41 (s, 3H).

$^13\text{C-NMR (101 MHz, CDCl}_3) \delta 212.04, 153.43, 147.98, 139.74, 123.34, 119.56, 111.41, 60.35, 55.75, 54.06, 43.20, 40.94, 36.02, 27.62, 22.19.$

HRMS (ESI+): Calculated mass $[\text{M+H}]^+$ $C_{15}H_{21}O_3^+ = 249.1485$; found: 249.1484.
Chiral HPLC analysis on a Chiracel OD-H column, $n$-Heptane : $i$-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 25.1 (minor) and 28.3 (major).

Chiral HPLC analysis on a Phenomenex LUX 5μ Cellulose-3 column, $n$-Heptane : $i$-PrOH = 99 : 1, 40 °C, flow = 1.0 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times for racemate (min): 12.4 and 14.7.

Chiral HPLC analysis on a Chiracel AD-H column, $n$-Heptane : $i$-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times for racemate (min): 23.1 and 28.7.

Chiral HPLC analysis on a Chiracel AD-H column, $n$-Heptane : $i$-PrOH = 99.5 : 0.5, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times for racemate (min): 16.5 and 17.9.

3-(2-methoxy-5-methylphenyl)-3-methylcyclohexanone (i):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 63% yield, enantioselective synthesis 28% yield, 91% ee.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.00 (s, 2H), 6.79 (d, $J = 8.9$, 1H), 3.80 (s, 3H), 2.99 (d, $J = 14.2$, 1H), 2.63 – 2.50 (m, 1H), 2.44 (d, $J = 13.6$, 1H), 2.31 (t, $J = 6.8$, 2H), 2.27 (s, 3H), 1.93 – 1.77 (m, 2H), 1.74 – 1.62 (m, 1H), 1.39 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 212.53, 155.83, 134.69, 129.68, 128.28, 127.95, 111.90, 55.13, 53.40, 42.73, 41.06, 35.12, 26.39, 22.25, 20.86.

HRMS (ESI+): Calculated mass [M+H]$^+$ $C_{15}H_{21}O_2^+$ = 233.1536; found: 233.1377.

[α]$^20_0 = +44.1$ (CHCl$_3$, $c = 0.01$) for a 91% ee sample.

Chiral HPLC analysis on a Chiracel AD-H column, $n$-Heptane : $i$-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 13.5 (minor) and 15.4 (major).
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Chiral HPLC analysis on a Chiracel OD-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 14.2 (major) and 16.0 (minor).

3-(2,5-dimethoxy-4-methylphenyl)-3-methylcyclohexanone (j):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 73% yield, enantioselective synthesis <10% yield using double catalyst loading 84% ee.

1H-NMR (400 MHz, CDCl₃) δ 6.73 (s, 1H), 6.70 (s, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.98 (d, J = 14.4, 1H), 2.68 – 2.57 (m, 1H), 2.41 (d, J = 14.4, 1H), 2.21 (t, J = 7.0, 2H), 2.19 (s, 3H), 1.91 – 1.81 (m, 1H), 1.81 – 1.73 (m, 1H), 1.65 – 1.55 (m, 1H), 1.40 (s, 3H).

13C-NMR (101 MHz, CDCl₃) δ 212.48, 151.39, 151.32, 132.40, 125.20, 115.22, 111.14, 56.04, 55.63, 53.97, 43.29, 41.05, 35.25, 27.07, 22.34, 15.85.

HRMS (ESI+): Calculated mass [M+H]⁺ C₁₆H₂₃O₂⁺ = 263.16417; found: 263.1644.

[α]D²⁰ = +18.7 (CHCl₃, c = 0.003) for a 84% ee sample.

Chiral HPLC analysis on a Phenomenex LUX 5μ Cellulose-3 column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 1.0 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 26.3 (minor) and 26.8 (major).

Chiral HPLC analysis on a Chiracel OD-H column, n-Heptane : i-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times for racemate (min): 21.4 and 22.3.
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3-(2-methoxy-4-methylphenyl)-3-methylcyclohexanone (4k):
This compound was prepared according to the general procedure and purified with flash chromatography using pentane : ether (4 : 1) as the eluent. Racemic synthesis = 76% yield, enantioselective synthesis = 17% yield, 90% ee.

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.08 (d, $J = 8.4$, 1H), 6.72 (d, $J = 6.9$, 2H), 3.82 (s, 3H), 2.98 (d, $J = 14.5$, 1H), 2.62 – 2.50 (m, 1H), 2.43 (d, $J = 14.3$, 1H), 2.32 (s, 3H), 2.29 (d, $J = 7.2$, 2H), 1.91 – 1.84 (m, 1H), 1.84 – 1.76 (m, 1H), 1.71 – 1.60 (m, 1H), 1.38 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 212.49, 157.71, 137.66, 131.84, 127.27, 121.12, 112.80, 54.90, 53.50, 42.56, 40.99, 35.12, 26.51, 22.21, 21.15.

HRMS (ESI+): Calculated mass [M+H]$^+$ C$_{15}$H$_{21}$O$_2$ = 233.15361; found: 233.15370. (ESI+): Calculated mass [M+Na]$^+$ C$_{15}$H$_{20}$O$_2$Na = 255.1355; found: 255.1356

$[\alpha]_D^{20} = +33.2$ (CHCl$_3$, $c = 0.01$) for a 90% ee sample.

Chiral HPLC analysis on a Chiracel OD-H column, $n$-Heptane : $i$-PrOH = 99 : 1, 40 °C, flow = 0.5 mL/min, UV detection at 190 nm, 225 nm and 254 nm, retention times (min): 23.5 (major) and 25.2 (minor).


5.7 References
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[8] As stated by the authors from reference 6 “Substituents at the 2-position of the arylboronic acid were detrimental to the yields and stereoselectivity of the reaction with enone (3-methyl hex-2-enone), although 2-fluorophenylboronic acid underwent the desired reaction to provide a product in 32% yield and
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77% ee”. Later work (see ref. 14) showed that the yield could be enhanced to 77% for the same transformation.


[11] The use of 7 eq of Michael acceptor resulted from the optimization of the conditions for the enantioselective transformation. Though not ideal, the enone is significantly cheaper than the boronic acids and could be easily retrieved in pure form by flash chromatography.


[15] The silver salt was changed to get the same counter-ion as reported by Stoltz et al. (see ref. 6 and 14).

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[17] For general strategies to mitigate protodeboronation, see reference 12b. For protodeboronation suppression by addition of excess of boronic acid see: a) Y. Takaya, M. Ogasawara, T. Hayashi, J. Am. Chem. Soc. 1998, 120, 5579. For protodeboronation suppression by temperature lowering see: b) T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, J. Am. Chem. Soc. 2002, 124, 5052. In our catalytic system an excess of arylboronic acid leads to significant biaryl formation. This product, in some cases, proved to be very difficult to separate from the desired Michael adduct. Lowering the reaction temperature led to significant retardation of the catalytic process.


[25] Over-oxidation was observed mainly in the form of benzylic oxidation.


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[30] Comparison of the optical rotation of the synthetic material with that of the natural source revealed that the absolute stereochemistry matched that of the natural product. Therefore we conclude that the conjugate addition of the boronic acid 4 to 3-methyl cyclopent-2-enone, using PdCl$_2$-(R,R-PhBOX), furnishes the Michael adducts with the (S)-configuration.


