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Enantioselective palladium catalyzed conjugate additions of *ortho*-substituted arylboronic acids to β,β -disubstituted cyclic enones: total synthesis of herbertenediol, enokipodin A and enokipodin B†

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The palladium-catalyzed conjugate addition (Michael addition) of *ortho*-substituted arylboronic acids to β,β -disubstituted cyclic enones, in particular 3-methyl cyclopent-2-enone and 3-methyl cyclohex-2-enone, is reported. With an achiral bipyridine-based palladium catalyst, good yields are obtained with a variety of *ortho*-substituted arylboronic acids. In the asymmetric version, good to very high enantiomeric excesses (up to 99% ee) are obtained, though the yields are moderate. The decreased yields are attributed to significant protodeboronation of the arylboronic acid. The developed methodology allows the efficient enantioselective synthesis of the very crowded, biologically active, sesquiterpenes herbertenediol, enokipodin A, and enokipodin B.

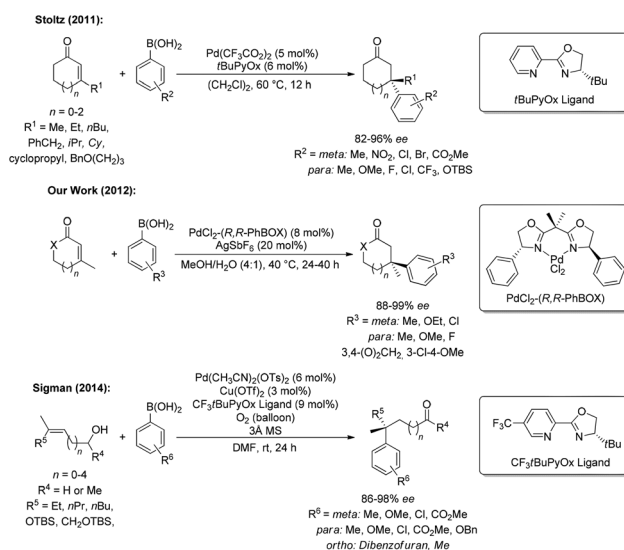
Introduction

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 β,β -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 β,β -disubstituted unsaturated electrophiles.³ Though addition of the corresponding arylaluminum 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 β,β -disubstituted unsaturated electrophile or in the organometallic reagent) is precarious, generally leading either to failure of the reaction, or low to moderate ee.^{3p,q,s,t} A notable exception has been reported by Hoveyda and co-workers who obtained excellent enantioselectivities (>95%) with anisole and *o*-tolyl aluminum reagents.^{3r} 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}

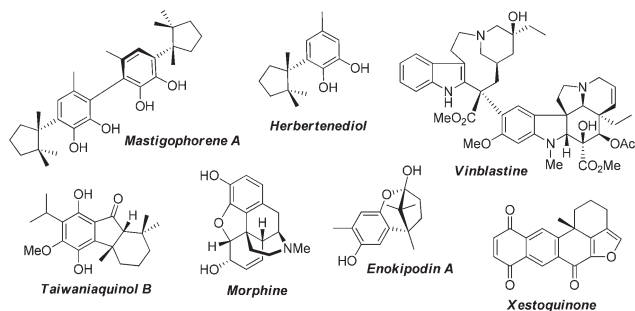
In 2011, the Stoltz laboratory reported the first asymmetric palladium-catalyzed conjugate addition of arylboronic acids to cyclic β -disubstituted enones using *t*BuPyOx as the ligand.⁶ Shortly thereafter we reported the asymmetric Michael addition of arylboronic acids to cyclic β -disubstituted enones and lactones, catalyzed by PdCl₂-(*R,R*-PhBOX) (Scheme 1).⁷



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

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Scheme 2 Selected natural products bearing *ortho*-substituted benzylic quaternary stereocenters.

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*-tolylboronic acid and dibenzofuran-4-boronic acid the yields dropped significantly to 35% and 25% respectively, showing the problems associated with *ortho*-substitution.

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 of 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 non-asymmetric fashion. The developed methodology is applied in the total synthesis of the sterically congested, biologically active, sesquiterpenes herbertenediol and enokipodin A and B.

Results and discussion

In a recent report,¹⁰ we showed efficient conjugate addition to cyclic β -substituted enones employing 1 mol% of a Pd(TFA)₂/2,2-bipyridine catalyst, two equivalents of boronic acid, at 60 °C for 18 h. Under these conditions the use of *ortho*-substi-

tuted 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)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 (Table 1).

As evident from Table 1, 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 acid low yields were obtained as well (20% and 12% respectively, entries 5 and 7). These low yields might be attributed to electronic effects, thus

Table 1 Pd-catalyzed conjugate addition of *ortho*-substituted arylboronic acids to β -methyl cyclic enones

| Entry | Boronic acid (R =) | Enone (n =) | Isolated yield (%) |
|-------|----------------------|-------------|----------------------|
| 1 | Me | 0 | 82 |
| 2 | Me | 1 | 41 |
| 3 | OMe | 0 | 69 |
| 4 | OMe | 1 | 55 |
| 5 | F | 0 | 20 (51) ^a |
| 6 | F | 1 | 7 (10) ^a |
| 7 | Cl | 0 | 12 (31) ^a |
| 8 | Cl | 1 | 8% |
| 9 | (HO) ₂ B- | 0 | 69 |
| 10 | | 1 | 14 (20) ^a |
| 11 | B(OH) ₂ - | 0 | 73 |
| 12 | | 1 | 20 (34) ^a |
| 13 | B(OH) ₂ - | 0 | 67 |
| 14 | | 1 | 44 |
| 15 | B(OH) ₂ - | 0 | 65 |
| 16 | | 1 | 17 (28) ^a |
| 17 | B(OH) ₂ - | 0 | 78 |
| 18 | | 1 | 63 |
| 19 | B(OH) ₂ - | 0 | 87 |
| 20 | | 1 | 73 |
| 21 | B(OH) ₂ - | 0 | 83 |
| 22 | | 1 | 76 |

^a The yield between brackets refers to reactions performed with 10 mol% of Pd(TFA)₂ and 15 mol% of 2,2-bipyridine.

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 (entries 2, 4 and 18) 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 (entry 8) only 8% of the desired product was isolated after two days of reaction, which clearly indicates the limits of this approach.

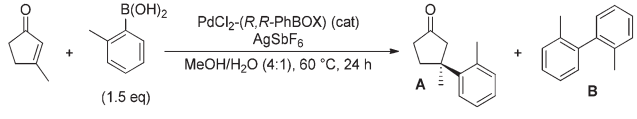
The conjugate addition of *ortho*-substituted arylboronic acids to 3-methyl cyclohept-2-enone was shortly investigated but did not lead to yields over 10% using 8 mol% of catalyst. This result is surprising to us since in our previously reported system, 3-methyl cyclohept-2-enone was tolerated as a substrate (using phenylboronic acid).¹⁰ 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,β -disubstituted enones accomplished, we envisioned the 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 PdCl₂-(*R,R*-PhBOX), and 40 mol% AgSbF₆ 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 2).

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* homocoupling 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,¹² and can be counter-balanced by changing the stoichiometry of the reaction, applying the reaction partner in excess.¹³ 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 seven equivalents.

During this optimization process, Stoltz and Houk reported a mechanistic investigation of the Pd-catalyzed asymmetric Michael addition of arylboronic acids to enones.¹⁴ It was shown that the chemical yields previously obtained, could be

Table 2 Optimization of the reaction conditions in the conjugate addition of *ortho*-tolylboronic acid to β -methyl cyclopentenone



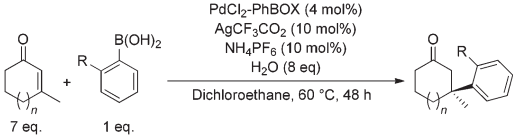
| Strategy | Catalyst loading | Silver salt | Additive(s) | A : B ratio ^a |
|--|------------------|---|---|--------------------------|
| Previous reported conditions ⁷ | 15 mol% | AgSbF ₆ (40 mol%) | None | 1 : 5 |
| Lewis acid activation | 15 mol% | AgSbF ₆ (40 mol%) | <i>i.e.</i> Sc(OTf) ₃ , Yb(OTf) ₃ , In(OTf) ₃ , Ce(OTf) ₃ (40 mol%) | 1 : 4 |
| Change of stoichiometry | 15 mol% | AgSbF ₆ (40 mol%) | 7 eq. of enone | 2.5 : 1 |
| Dichloroethane as solvent | 15 mol% | AgCF ₃ CO ₂ (40 mol%) | NH ₄ PF ₆ (40 mol%) | 20 : 1 |
| Lowering the catalyst loading ^b | 8 mol% | AgCF ₃ CO ₂ (20 mol%) | NH ₄ PF ₆ (20 mol%) | 18 : 1 |
| | 4 mol% | AgCF ₃ CO ₂ (10 mol%) | NH ₄ PF ₆ (10 mol%) | 12 : 1 |
| | 4 mol% | AgPF ₆ (10 mol%) | None | 3.5 : 1 |

^a The ratio was determined by GC/MS analysis. ^b Water (8 eq.) was added as an additive.

enlarged by adding NH₄PF₆ (30 mol%) and water (5 eq.) to their system. We adopted these conditions by changing the solvent from MeOH–H₂O to dichloroethane, and the silver salt from AgSbF₆ to AgCF₃CO₂ to obtain a similar system, still using 7 eq. of the enone.¹⁵ 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 (AgCF₃CO₂ and NH₄PF₆) by combining them in the form of AgPF₆. 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 (Table 3). 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 (entries 4, 6, 7, 11, 17, 19), 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 (entries 11 *vs.* 12, 15 *vs.* 16, 17 *vs.* 18 and 21 *vs.* 22) 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 (Table 2). It is also notable that the conjugate additions to 3-methyl cyclohex-2-enone give equal or higher enantiomeric excesses (up to 22%

Table 3 Asymmetric Pd-catalyzed conjugate addition of arylboronic acids to β -methyl cyclic enones

|  | | | | |
|---|---------------------|-------------|----------------------|---------------------|
| Entry | Boronic acid (R =) | Enone (n =) | Isolated yield (%) | ee ^a (%) |
| 1 | Me | 0 | 23 | 90 |
| 2 | Me | 1 | 16 | 98 |
| 3 | OMe | 0 | 45 | 80 |
| 4 | OMe | 1 | 20 (42) ^b | 96 |
| 5 | F | 0 | 20 | 95 |
| 6 | F | 1 | 13 (23) ^b | 95 |
| 7 | Cl | 0 | 8 (12) ^b | 94 |
| 8 | Cl | 1 | n.d. ^c | n.d. ^c |
| 9 | (HO) ₂ B | 0 | 51 | 93 |
| 10 | | 1 | 36 | 93 |
| 11 | | 0 | 20 (38) ^b | 85 |
| 12 | | 1 | 26 | 95 |
| 13 | | 0 | 36 (55) ^b | 92 |
| 14 | | 1 | 19 | 94 |
| 15 | | 0 | 25 | 94 |
| 16 | | 1 | 44 | 99 |
| 17 | | 0 | 19 (32) ^b | 80 |
| 18 | | 1 | 28 | 91 |
| 19 | | 0 | 12 (21) ^b | 74 |
| 20 | | 1 | n.d. ^c | 84 |
| 21 | | 0 | n.d. ^c | 68 |
| 22 | | 1 | 17 | 90 |

^a Enantiomeric excess was determined using chiral HPLC analysis.^b The yield between brackets refers to reactions performed with double catalyst loading (8 mol%). ^c n.d. = not determined, the yield of these reaction is <10%. For the absolute configuration see ref. 30.

ee higher, entry 21 vs. 22) 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 might be the consequence of steric hindrance. The chiral environment of the catalyst allows "easy" access of the cyclopentenone (resulting in a 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 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 con-

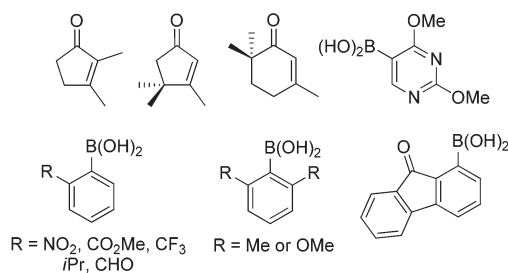
jugate addition, protodeboronation^{16a,12b} might be associated with: (1) Pd-catalyzed protodeboronation,^{16c} (2) Ag-catalyzed protodeboronation,^{16d-h} (3) heat-induced protodeboronation,^{16ij} (4) fluoride-mediated protodeboronation (with PF₆⁻ as a potential F⁻ source),^{16k,l} (5) acid-catalyzed 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.⁹ For their asymmetric Pd-catalyzed remote benzylic quaternary stereocenter formation using arylboronic acids, the yields are typically 50–80%, however when using *o*-tolylboronic 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 (Fig. 1). It is not surprising that larger *ortho*-substituents such as CHO, NO₂, CF₃, *i*Pr and CO₂Me impeded the reaction. In addition, di-*ortho* substitution was not tolerated. Variation of the five-membered enone in terms of substitution at the α - or γ -position also led to failure of reaction, as did substituting the α' -position of 3-methyl cyclohex-2-enone with a geminal dimethyl moiety.

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 (1), enokipodin A (2), and B (3). Herbertenediol (1) is a sesquiterpene isolated from the liverworts *Herberta adunca*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 μ g mL⁻¹).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.*^{21fg} The Bringmann laboratory employed a kinetic resolution,^{21b} as did the Monti group,^{21h} to furnish enantiopure material. Meyers^{21a} and

**Fig. 1** Unreactive substrates and boronic acids in the Pd-catalyzed asymmetric Michael addition.

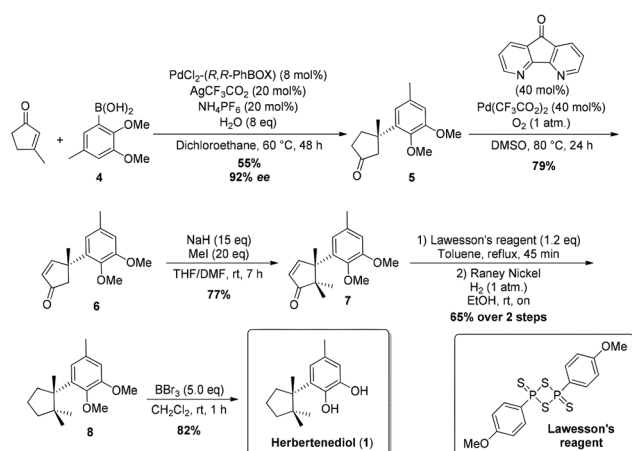
Fukuyama^{21c} relied on the use of a chiral auxiliary. We reasoned that direct introduction of the quaternary stereocenter by means of an asymmetric conjugate addition of a suitable substituted phenylboronic acid allowed to shorten the synthesis of herbertenediol considerably.

The synthesis of herbertenediol started with the asymmetric conjugate addition of 2,3-dimethoxy-5-methyl phenylboronic acid to 3-methyl cyclopentenone employing 8 mol% of $\text{PdCl}_2-(R,R\text{-PhBOX})$, and afforded the desired Michael adduct **5** in 55% yield and high enantioselectivity (92% ee, Scheme 3). In order to selectively install the geminal dimethyl moiety without generating (hard to separate) regioisomers, **5** was subjected to an oxidative dehydrogenation. Initially, several stoichiometric oxidation procedures (DDQ,²² IBX,²³ and iodic acid²⁴) were applied, which led to low isolated yields (<30%) and over-oxidized products.²⁵ A suitable alternative was found in the $\text{Pd}(\text{TFA})_2/4,5\text{-diazfluorenone}$ catalyzed oxidation, recently developed by Stahl and co-workers.²⁶ Stahl reported cyclopentenone oxidation with oxygen (7.2 bar, 9% in N_2) using 5 mol% of catalyst, whereas catalyst decomposition was observed at atmospheric pressure. Also in the current case, oxidation of **5** 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 **6**.

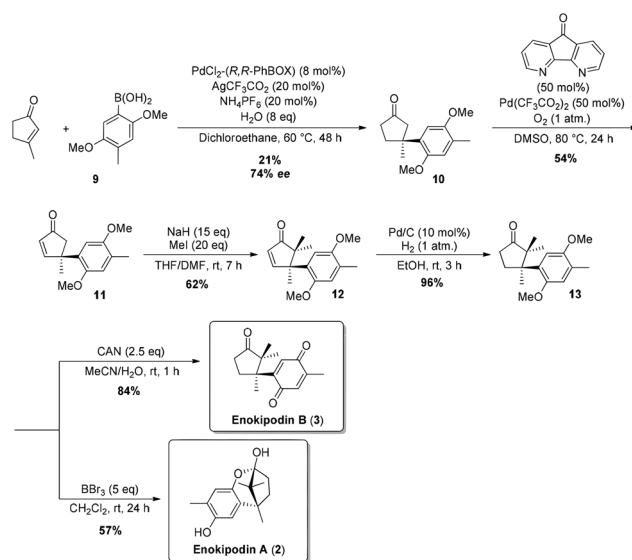
With **6** in hand, a one-pot geminal dimethylation as described by Srikrishna was employed yielding 77% of **7**.²⁷ In order to acquire fully reduced product **8**, several procedures were considered. Deoxygenation by means of a classic Wolff-Kishner reduction was reported to be problematic in related systems and was therefore rejected.²⁸ Deoxygenation employing a Mozingo reduction (thioketalization/RANEY® nickel desulfurization with the saturated analogue of **7**) 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 for-

mation, 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 **7** was converted into the corresponding thio-ketone and was subsequently reduced with RANEY® nickel (Ra/Ni), leading to **8** in 58% yield over the two steps.^{21a} This strategy proved to be reproducible in our hands, providing us with **8** 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 H_2 is adsorbed on the catalyst) compared to commercial Ra/Ni (no absorbed H_2 for safe shipment). Demethylation using BBr_3 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 pose 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}



Scheme 3 Asymmetric total synthesis of herbertenediol.



Scheme 4 Asymmetric total synthesis of enokipodin A and enokipodin B.

Our synthesis of enokipodin A and B started with the asymmetric Michael addition of boronic acid **9** to 3-methyl cyclopent-2-enone, yielding **10** in 21% yield and a good enantioselectivity of 74% ee (Scheme 4). Introduction of the α,β -unsaturation was subsequently achieved using the previously described Pd(TFA)₂/4,5-diazafluorenone catalyzed oxidation, in 54% yield. Dimethylation followed by hydrogenation of enone **12** gave ketone **13** (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 **13** 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.

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 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, enokipodin A and enokipodin B was achieved with routes that are considerably shorter than previously reported.

Acknowledgements

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Notes and references

- 1 *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, ed. J. Christoffers and A. Baro, Wiley-VCH, Weinheim, 2005. For selected reviews on the synthesis of quaternary stereocenters, see: (a) I. Denissova and L. Barriault, *Tetrahedron*, 2003, **59**, 10105; (b) C. J. Douglas and L. E. Overman, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5363; (c) J. Christoffers and A. Baro, *Adv. Synth. Catal.*, 2005, **347**, 1473; (d) B. M. Trost and C. Jiang, *Synthesis*, 2006, 369; (e) J. T. Mohr and B. M. Stoltz, *Chem. – Asian J.*, 2007, **2**, 1476; (f) P. G. Cozzi, R. Hilgraf and N. Zimmermann, *Eur. J. Org. Chem.*, 2007, 5969; (g) J. P. Das and I. Marek, *Chem. Commun.*, 2011, **47**, 4593.
- 2 C. Hawner and A. Alexakis, *Chem. Commun.*, 2010, **46**, 7295. See also: A. Alexakis, N. Krausse and S. Woodward, in *Copper-catalyzed Asymmetric Synthesis*, ed. A. Alexakis, N. Krausse and S. Woodward, Wiley-VCH, Weinheim, 2014, ch. 2.
- 3 For Selected examples: (a) K. P. McGrath and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2014, **53**, 1910; (b) D. Willcox, S. Woodward and A. Alexakis, *Chem. Commun.*, 2014, **50**, 1655; (c) D. Müller and A. Alexakis, *Chem. – Eur. J.*, 2013, **19**, 15226; (d) D. Müller and A. Alexakis, *Org. Lett.*, 2013, **15**, 1594; (e) C. Bleschke, M. Tissot, D. Müller and A. Alexakis, *Org. Lett.*, 2013, **15**, 2152; (f) J. A. Dabrowski, M. T. Villaume and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2013, **52**, 8156; (g) J. A. Dabrowski, F. Haeffner and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2013, **52**, 7694; (h) D. Müller and A. Alexakis, *Chem. Commun.*, 2012, **48**, 12037; (i) D. Müller, M. Tissot and A. Alexakis, *Org. Lett.*, 2011, **13**, 3040; (j) M. Tissot, A. Pérez Hernández, D. Müller, M. Mauduit and A. Alexakis, *Org. Lett.*, 2011, **13**, 1524; (k) T. L. May, J. A. Dabrowski and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2011, **133**, 736; (l) C. Hawner, D. Müller, L. Gremaud, A. Felouat, S. Woodward and A. Alexakis, *Angew. Chem., Int. Ed.*, 2010, **49**, 7769; (m) A. Wilsily and E. Fillion, *J. Org. Chem.*, 2009, **74**, 8583; (n) A. Wilsily and E. Fillion, *Org. Lett.*, 2008, **10**, 2801; (o) E. Fillion and A. Wilsily, *J. Am. Chem. Soc.*, 2006, **128**, 2774; (p) A. Wilsily and E. Fillion, *J. Org. Chem.*, 2009, **74**, 8583; (q) C. Hawner, K. Li, V. Cirriez and A. Alexakis, *Angew. Chem., Int. Ed.*, 2008, **47**, 8211; (r) T. L. May, M. K. Brown and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2008, **47**, 7358; (s) M. Vuagnoux-d'Augustin and A. Alexakis, *Chem. – Eur. J.*, 2007, **13**, 9647; (t) E. Fillion and A. Wilsily, *J. Am. Chem. Soc.*, 2006, **128**, 2774.
- 4 (a) R. Shintani, W.-L. Duan and T. Hayashi, *J. Am. Chem. Soc.*, 2006, **128**, 5628; (b) R. Shintani, Y. Tsutsumi, M. Nagaosa, T. Nishimura and T. Hayashi, *J. Am. Chem. Soc.*, 2009, **131**, 13588; (c) R. Shintani, M. Takeda, T. Nishimura and T. Hayashi, *Angew. Chem., Int. Ed.*, 2010, **49**, 3969; (d) R. Shintani and T. Hayashi, *Org. Lett.*, 2011, **13**, 350.
- 5 For reports on quaternary stereocenter formation using arylboronic acids see: (a) P. Mauleón and J. C. Carretero, *Chem. Commun.*, 2005, 4961; (b) B. T. Hahn, F. Tewes, R. Fröhlich and F. Glorius, *Angew. Chem., Int. Ed.*, 2010, **49**, 1143.
- 6 K. Kikushima, J. C. Holder, M. Gatti and B. M. Stoltz, *J. Am. Chem. Soc.*, 2011, **133**, 6902.
- 7 A. L. Gottumukkala, K. Matcha, M. Lutz, J. G. de Vries and A. J. Minnaard, *Chem. – Eur. J.*, 2012, **18**, 6907.
- 8 As stated by the authors from ref. 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 77% ee". Later work (see ref. 14) showed that the yield could be enhanced to 77% for the same transformation.

- 9 T.-S. Mei, H. H. Pater and M. S. Sigman, *Nature*, 2014, **508**, 340.
- 10 (a) A. L. Gottumukkala, J. Suljagic, K. Matcha, J. G. de Vries and A. J. Minnaard, *ChemSusChem*, 2013, **6**, 1636; (b) For a similar transformation see: S. Lin and X. Lu, *Org. Lett.*, 2010, **12**, 2536.
- 11 The use of 7 eq. of Michael acceptor resulted from the optimization of the conditions for the enantioselective transformation (*vide infra*). Though not ideal, the enone is significantly cheaper than the boronic acids and could be easily retrieved in pure form by flash chromatography.
- 12 Undesired Pd-catalyzed homo-coupling as a side-product is mentioned in: (a) G. A. Molander and B. Biolatto, *J. Org. Chem.*, 2003, **68**, 4302; (b) A. J. J. Lennox and G. C. Lloyd-Jones, *Isr. J. Chem.*, 2010, **50**, 664; (c) A. J. J. Lennox and G. C. Lloyd-Jones, *Chem. Soc. Rev.*, 2014, **43**, 412.
- 13 Homo-coupling suppression by using an excess of boronic acid is mentioned in: M. S. Wong and X. L. Zhang, *Tetrahedron Lett.*, 2001, **42**, 4087.
- 14 J. C. Holder, L. Zou, A. N. Marziale, P. Liu, Y. Lan, M. Gatti, K. Kikushima, K. N. Houk and B. M. Stoltz, *J. Am. Chem. Soc.*, 2013, **135**, 14996.
- 15 The silver salt was changed to get the same counter-ion as reported by Stoltz *et al.* (see ref. 6 and 14).
- 16 For general remarks on protodeboronation (a) D. G. Hall, in *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials – Second Completely Revised Edition*, ed. D. G. Hall, Wiley-VCH, Weinheim, 2011, ch. 1; (b) See ref. 12b. For specific types of protodeboronation reactions see: (1) *Pd-catalyzed protodeboronation*: (c) H. G. Kuivila, J. F. Reuwer Jr. and J. A. Mangravite, *J. Am. Chem. Soc.*, 1964, **86**, 2666 (2) *Ag-catalyzed protodeboronation*: (d) A. Michaelis and P. Becker, *Chem. Ber.*, 1882, **15**, 180; (e) W. Seaman and J. R. Johnson, *J. Am. Chem. Soc.*, 1931, **53**, 711; (f) J. R. Johnson, M. G. van Campen Jr. and O. Grummitt, *J. Am. Chem. Soc.*, 1938, **60**, 111; (g) H. G. Kuivila, J. F. Reuwer Jr. and J. A. Mangravite, *J. Am. Chem. Soc.*, 1964, **86**, 2666; (h) C. Pourbaix, F. Carreaux, B. Carboni and H. Deleuze, *Chem. Commun.*, 2000, 1275; (3) *Heat induced protodeboronation*: (i) M. A. Beckett, R. J. Gilmore and K. Idrees, *J. Organomet. Chem.*, 1993, **455**, 47; (j) C.-Y. Lee, S.-J. Ahn and C.-H. Cheon, *J. Org. Chem.*, 2013, **78**, 12154; (4) *Fluoride mediated protodeboronation*: (k) S. Nave, R. P. Sonawane, T. G. Elford and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2010, **132**, 17096; (l) M. J. Hesse, C. P. Butts, C. L. Willis and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2012, **51**, 12444; (5) *Acid-catalyzed protodeboronation*: (m) H. G. Kuivila and K. V. Nahabedian, *J. Am. Chem. Soc.*, 1961, **83**, 2159; (n) H. G. Kuivila and K. V. Nahabedian, *J. Am. Chem. Soc.*, 1961, **83**, 2164; (o) K. V. Nahabedian and H. G. Kuivila, *J. Am. Chem. Soc.*, 1961, **83**, 2167; (6) *Protodeboronation by hydrolysis*: (p) A. D. Ainley and F. Challenger, *J. Chem. Soc.*, 1930, 2171.
- 17 For general strategies to mitigate protodeboronation, see ref. 12b; For protodeboronation suppression by addition of excess of boronic acid see: (a) Y. Takaya, M. Ogasawara and T. Hayashi, *J. Am. Chem. Soc.*, 1998, **120**, 5579. For protodeboronation suppression by temperature lowering see: (b) T. Hayashi, M. Takahashi, Y. Takaya and 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.
- 18 A. Matsuo, S. Yuki and M. Nakayama, *J. Chem. Soc., Perkin Trans.*, 1986, 701.
- 19 M. Toyota, T. Kinugawa and Y. Asakawa, *Phytochemistry*, 1994, **37**, 859.
- 20 Y. Fukuyama, Y. Kiriya and M. Kodama, *Tetrahedron Lett.*, 1996, **37**, 1261.
- 21 Asymmetric total syntheses of herbertenediol: (a) A. P. Degnan and A. I. Meyers, *J. Am. Chem. Soc.*, 1999, **121**, 2762; (b) G. Bringmann, T. Pabst, P. Henschel, J. Kraus, K. Peters, E.-M. Peters, D. S. Rycroft and J. D. Connolly, *J. Am. Chem. Soc.*, 2000, **122**, 9127; (c) Y. Fukuyama, K. Matsumoto, Y. Tono, R. Yokoyama, H. Takahashi, H. Minami, H. Okazaki and Y. Mitsumoto, *Tetrahedron*, 2001, **57**, 7127; (d) A. Abad, C. Agulló, A. C. Cuñat, D. Jiménez and R. H. Perni, *Tetrahedron*, 2001, **57**, 9727; (e) A.-M. Zhang and G.-Q. Lin, *Chin. J. Chem.*, 2001, **19**, 1245; (f) Y. Kita, J. Futamura, Y. Ohba, Y. Sawama, J. K. Ganesh and H. Fujioka, *J. Org. Chem.*, 2003, **68**, 5917; (g) Y. Kita, J. Futamura, Y. Ohba, Y. Sawama, J. K. Ganesh and H. Fujioka, *Tetrahedron Lett.*, 2003, **44**, 411; (h) S. Achcar, G. Audran, F. Fotiadu and H. Monti, *Eur. J. Org. Chem.*, 2004, 5092. For racemic syntheses see: (i) Y. Fukuyama, Y. Kiriya and M. Kodama, *Tetrahedron Lett.*, 1996, **37**, 1261; (j) P. D. Gupta, A. Pal, A. Roy and D. Mukherjee, *Tetrahedron Lett.*, 2000, **41**, 7563; (k) Y. Fukuyama, K. Matsumoto, Y. Tono, R. Yokoyama, H. Takahashi, H. Minami, H. Okazaki and Y. Mitsumoto, *Tetrahedron*, 2001, **57**, 7127; (l) A. Srikrishna and M. S. Rao, *Tetrahedron Lett.*, 2001, **42**, 5781; (m) A. Srikrishna and M. S. Rao, *Synlett*, 2002, 340; (n) A. Srikrishna and G. Satyanarayana, *Tetrahedron*, 2006, **62**, 2892.
- 22 H. E. Zimmerman and R. D. Little, *J. Am. Chem. Soc.*, 1974, **96**, 4623.
- 23 K. C. Nicolaou, T. Montagnon, P. S. Baran and Y.-L. Zhong, *J. Am. Chem. Soc.*, 2002, **124**, 2245.
- 24 K. C. Nicolaou, T. Montagnon and P. S. Baran, *Angew. Chem., Int. Ed.*, 2002, **41**, 1386.
- 25 Over-oxidation was observed mainly in the form of benzylic oxidation.
- 26 T. Diao, T. J. Wadzinski and S. S. Stahl, *Chem. Sci.*, 2012, **3**, 887.
- 27 A. Srikrishna and P. C. Ravikumar, *Tetrahedron*, 2006, **62**, 9393.
- 28 (a) D. H. R. Barton, D. A. J. Ives and B. R. Thomas, *J. Chem. Soc.*, 1955, 2056; (b) D. H. R. Barton, D. A. J. Ives and B. R. Thomas, *J. Chem. Soc.*, 1954, 903.

- 29 M. Yoshida, T. Kasai, T. Mizuguchi and K. Namba, *Synlett*, 2014, **25**, 1160.
- 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 PdCl₂-(*R,R*-PhBOX), furnishes the Michael adducts with the (*S*)-configuration.
- 31 N. K. Ishikawa, K. Yamaji, S. Tahara, Y. Fukushi and K. Takahashi, *Phytochemistry*, 2000, **54**, 777.
- 32 N. K. Ishikawa, Y. Fukushi, K. Yamaji, S. Tahara and K. Takahashi, *J. Nat. Prod.*, 2001, **64**, 932.
- 33 For asymmetric enokipodin A and B syntheses see: (a) K. P. McGrath and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2014, **53**, 1910; (b) M. Yoshida, Y. Shoji and K. Shishido, *Org. Lett.*, 2009, **11**, 1441; (c) M. Saito and S. Kuwahara, *Biosci., Biotechnol., Biochem.*, 2005, **69**, 374; (d) S. Kuwahara and M. Saito, *Tetrahedron Lett.*, 2004, **45**, 5047. For racemic syntheses see: (e) A. Srikrishna and M. S. Rao, *Synlett*, 2004, 374; (f) F. Secci, A. Frongia, J. Ollivier and P. P. Piras, *Synthesis*, 2007, 999; (g) J. A. Luján-Montelongo and J. G. Avila-Zarraga, *Tetrahedron Lett.*, 2010, **51**, 2232; (h) D. Lebœuf, C. M. Wright and A. J. Frontier, *Chem. – Eur. J.*, 2013, **19**, 4835.