A catalytic asymmetric cross-coupling approach to the synthesis of cyclobutanes

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Abstract

Stereodefined four-membered rings are common motifs in bioactive molecules and versatile intermediates in organic synthesis. However, the synthesis of complex, chiral cyclobutanes is a largely unsolved problem and there is a need for general and modular synthetic methods. Here we report a series of asymmetric cross-coupling reactions between cyclobutenes and arylboronic acids which are initiated by Rh-catalysed asymmetric carbometallation. After the initial carborhodation, Rh-cyclobutyl intermediates undergo chain-walking or C–H insertion so that overall a variety of additions such as reductive Heck reactions, 1,5-addition and homo-allylic substitution are observed. The synthetic applicability of these highly stereoselective transformations is demonstrated in the concise syntheses of the drug candidates Belaperidone and PF-04862853. We anticipate this approach will be widely adapted by synthetic and medicinal chemists, and while the carbometallation approach is here exemplified with Rh and arylboronic acids, it is likely applicable to other metals and nucleophiles.

Introduction

Stereochemically complex, chiral cyclobutanes are found in many natural products and medical drugs (Fig. 1a), and are strategically useful intermediates in organic synthesis^{1–5}. Methods to access enantiomerically enriched cyclobutanes involve enantiospecific and enantioselective cyclisation reactions, functionalisation of preformed 4-membered rings, or multistep ring-contraction and expansion strategies¹. Catalytic enantioselective syntheses of cyclobutanes are rare, and most existing methods can be classified into two categories – enantioselective ring closure and the

functionalisation of preformed rings. Enantioselective ring closure strategies include photochemical and metal-catalysed [2+2] addition reactions^{6–10}, and cyclisation strategies^{11,12} but are limited to specific substrate classes and substitution patterns. Alternatively, preformed 4-membered rings can be functionalised by directing-group controlled C–H activation strategies¹³, and addition reactions to activated cyclobutenes have been developed^{14–16}.

Carbometallation processes are among the most fundamental processes in asymmetric catalysis and are often triggered by the release of ring strain, but such a process is previously unknown for unactivated cyclobutenes. While copper-catalysed asymmetric hydroboration and hydroamination are known to add heteroatom nucleophiles to cyclobutenes^{17,18}, the asymmetric addition of carbon-nucleophiles *via* carbometallation to form new carbon-carbon bonds remains elusive¹⁹. Even non-enantioselective carbometallation approaches for four-membered rings are non-trivial and rare¹⁹, and strategies that work very well for more strained species like cyclopropenes do not generally translate to cyclobutenes²⁰.

Addition reactions across double bonds can be triggered by electron-withdrawing groups in the allylic position, this strategy is prevalent in 1,4-addition reactions. Rhodium-catalysed asymmetric addition of arylboronic acids to α,β -unsaturated ketones²¹, many electron-deficient alkenes²² and allyl halides^{23,24} have made enantioselective arylations powerful tools for generating C(sp²)-C(sp³) bonds with stereochemical control. Boronic acid nucleophiles are often commercially available, and easy to handle²⁵, and these factors have led to their extensive use in drug discovery²⁶. Reductive Heck reactions of unfunctionalised alkenes that utilize the release of olefinic-strain have been reported for cyclopropenes (27.7 kcal/mol)^{27,28} and (di-)azabicycles (for norbornene: 4.8 kcal/mol)^{28–30} and also hydroarylation of pyrrolines is known³¹. These reports stimulated our interest in whether the relatively small olefinic-strain of cyclobutenes (1.9 kcal/mol)²⁸ is sufficient to drive rhodium-catalysed arylation of cyclobutenes.

Here we present rhodium-catalysed carbometallation reactions of diverse cyclobutenes with boronic acid nucleophiles (Fig. 1b). All these reactions share a common cyclobutyl rhodium complex as catalytic intermediate, which is formed in an enantioselective carbometallation step (Fig. 1b, centre). Depending on the cyclobutene, this common intermediate can diverge into different pathways leading to different types of products. We found that *meso*-bicyclic cyclobutenes undergo highly enantioselective reductive Heck reactions in which the terminating protonation step occurs remote to the addition-site *via* chain-walking (1). Carborhodation and subsequent chain-walking can also trigger stereoselective 1,5-additions to bicyclic and mono-cyclic β,γ -unsaturated carbonyl compounds (2 and 3) and homo-allylic substitution reactions (4). An alternative protonation pathway *via* C–H insertion enables reductive Heck reaction to mono-cyclic cyclobutenes (5). High regioselectivity for achiral products is obtained for non-symmetrical cyclobutenes (6). We discuss mechanistic aspects of these transformations and demonstrate their synthetic utility.

Results and Discussion

Reductive Heck reactions *via* chain-walking

The D4/5-HT2 antagonist Belaperidone exhibits a 6-aryl-3-azabicyclo[3.2.0]heptane core (see Fig 1a)³² and we envisioned that this motif could be made enantioselectively *via* a reductive Heck reaction. We found several sets of conditions that enable the addition of arylboronic acids to cyclobutene **1** at room temperature (23 °C) in the absence of base. An *in situ* generated Rh/Segphos catalyst provides excellent enantioselectivity and good to moderate yields for a range of functionalised *meta*- and *para*-substituted arylboronic acids (Table 1, **3a–3m**). Several functional groups including halides (**3d–e**, **3g**) that can serve as handles for subsequent complementary cross-coupling reactions, (thio-)alkoxides (**3b–c**, **3f**), and also a pyrazole (**3k**) were tolerated. Lower yields were obtained with some boronic acids with electron-withdrawing groups in the *para*-position (**3g–3i**). With *ortho*-substituted arylboronic acids, which often suffer from low yields and

enantioselectivity in transition metal catalysed reactions³³, we obtained low enantioselectivity using standard conditions (52% e.e. for **3n**) but simply using (*S*)-BINAP instead of (*S*)-Segphos gave improved results (80% e.e.; Table 1). Several electron-rich heterocyclic coupling partners gave good results when using (*S*)-DTBM-Segphos (Table 1, **3p-3s**). Moderate enantioselectivity was observed for 3-thiopheneboronic acid and very low enantioinduction was achieved for furan derived boronic acids with our current catalytic systems. Cyclobutenes with complementary *N*-protecting groups were tolerated (Table 1, **3aa-3ba**) as were cyclobutenes fused with a sulfone and cyclopentanones (**3ca-3da**).

Having established several hydroarylation reactions with bicyclic cyclobutenes, we aimed to uncover the underlying mechanism. In addition to desired cyclobutane **3a**, we isolated di-cyclobutane **3a'** (Fig. 2a) as a major side-product. Similar side-products were formed with most other boronic acids, causing particularly poor yields for **3h-3k**. A reaction performed in D₂O gave **3a-C2-d** with exclusive deuterium incorporation at the C(2) position (see Fig. 2a)³¹. To explain the reactivity and selectivity patterns, we propose a mechanism (Fig. 2a) initiated by transmetallation of PhB(OH)₂ acid and Rh-OH complex **I** to give **II**³⁴. Next, the cyclobutene undergoes rhodoarylation with **II** *anti* to the other cyclobutene substituents to set the absolute stereochemistry and give the Rh-alkyl complex **III**. Intermediate **III** can then engage in two pathways. A chain-walking process can occur *via* reversible β -hydride elimination and subsequent 1,2-hydride shifts to give rhodium alkyl complex **IV** (Fig. 2b; alternatively, chain-walking could occur *via* a 1,3-hydride shift from **VI** to **VIII**)³⁵. Remarkably, the chain-walking occurs over the bridgehead of a fused bicycle. Protonation of **IV** with H₂O liberates the product **3** and regenerates catalyst **I**. Dimers such as **3a'** likely arise through an alternative pathway where in **III** Rh-inserts in the *ortho*-aryl C–H bond to give Rh-aryl complex **V**³⁵, and another rhodoarylation with a second cyclobutene gives dimeric side-product **3a'**. As no deuterium incorporation was observed at the C(2') position, we concluded that the C–H insertion pathway exclusively leads to the dimeric side-product and protonation of **V** is not an effective quenching mechanism. Di-*meta*-substitution, which shields the *ortho* C–H positions from insertion,

was found to completely suppress the dimerization pathway and **3m** was obtained in quantitative yield (Table 1).

Asymmetric 1,5-additions triggered by carbometallation

Intrigued by the chain-walking mechanism proposed above, we explored whether we could perform an asymmetric 1,5-addition to substituted cyclobutenes (Table 2). In reactions with non-conjugated β,γ -unsaturated carbonyl **4** we found using (*S*)-DTBM-Segphos and increasing the temperature to 60 °C was required to achieve good yields and consistent enantioselectivity with a range of (hetero-)arylboronic acids (**5a-5j**). These conditions are not suitable for *ortho*-substituted arylboronic acids.

Performing the reaction to form **5a** with D₂O resulted in 88% deuterium incorporation at the C(1) position. While the first two steps of the catalytic cycle likely occur *via* the same transmetallation and carbometallation sequence as with substrate **1** (Fig. 2a), here we propose that an oxa- π -allyl Rh-complex **XI** (Fig. 3a) is formed *via* a β -hydride elimination/ conjugated 1,4-hydride-addition sequence³⁴. The formation of a relatively stable oxa- π -allyl complex likely serves as a better thermodynamic sink to suppresses the competitive dimerization pathway observed with **1** (Fig. 2a), and the yields with **4** are essentially independent of the electronics of the arylboronic acid.

Ring fusion favours the *cis* configuration, which controls the diastereoselectivity observed during protonation of the oxa- π -allyl Rh-complex **XI**. The hydroarylation of *cis*-diester **6** was found to give **7**, with the major *trans-trans*-diastereomers isolated in pure form (Fig. 3b), demonstrating that diastereoselective protonation of oxa- π -allyl Rh-complexes allows for remote stereocontrol.

While cyclobutenes **1** and **4** are *meso* compounds, a racemic mixture of ($\pm$)-**8** afforded enantioenriched **9** and **9'** in roughly a 1:1 mixture (Fig. 3c). As each enantiomer of the starting material undergoes a different reaction pathway that leads to regioisomeric products (Fig. 3c, *via* intermediates **XII** and **XII'**), this is an example of a regiodivergent reaction on a racemic mixture³⁷.

Divergent reactions on racemic mixtures are practical alternatives to kinetic resolutions, and in this case, the products can be separated by flash column chromatography.

To establish the synthetic practicality of our method, we developed two highly enantioselective catalytic approaches towards Belaperidone (Fig. 3d). Previously reported non-racemic syntheses rely on chiral resolution *via* crystallization^{38,39} and chiral auxiliaries for diastereomeric separation⁴⁰. Our rhodium-catalysed addition of 4-fluorophenylboronic to cyclobutenes **1** or **4** and subsequent removal of the protecting groups give access to amine **10** – a key intermediate in the synthesis of Belaperidone^{36,37}. While the sequence *via* **5h** is higher yielding, an alternative route *via* **3h** allows for later introduction of the aryl group facilitating efficient analogue syntheses. The key rhodium catalysed additions of 4-fluorophenylboronic acid to **4** can easily be scaled-up to gram quantities, and we were able to decrease the catalyst loading from 2.5 to 0.5 mol% of dimeric [Rh(cod)OH]₂ to give 1.3 g of **5h** (72%, 98% e.e.).

Regioselective reductive Heck *via* C–H insertion

The challenge of achieving high regioselectivity in the carbometallation of non-symmetrical cyclobutenes attracted our attention, and we chose the drug-like, spirocyclic **12** as model substrate. Complete regioselectivity for achiral **13** was obtained. Optimal results were achieved with an achiral Rh/dppf catalyst with CsOH as a base at 60 °C for a range of (hetero-)arylboronic acids (Table 3, **13a–13j**). Dimeric compounds analogous to **3a'** were the only observed side-products (see Supporting Information, p.S60, **13a'**) and in some cases (e.g **13b**, **13g**) unreacted cyclobutene was still present. This method enables a concise and modular formal synthesis of the fatty acid amide hydrolase (FAAH) inhibitor drug candidate PF-04862853 (**14**) (Fig. 4a)⁴¹.

In contrast to the systems above, here the deuteration occurs at the C(2') position *via* a C–H insertion pathway. While an unsymmetrical intermediate is formed by carbometallation, the chirality is lost in the subsequent C–H insertion process to give an achiral product (Fig. 4b). In order to investigate the diastereoselectivity in this regioselective reductive Heck reaction, (±)-**12a** was

subjected to our standard reaction conditions which afforded **13aa** with a diastereomeric ratio of 4:1, displaying the potential to develop other diastereoselective transformations (Fig. 4c).

Remote Substitution

In the reactions above, after carbometallation, protonation of the Rh-cyclobutyl intermediates was accomplished *via* processes involving C–H insertion or chain-walking. Inspired by the 1,5-addition process above, we decided to investigate if this addition strategy to non-conjugated olefins was suitable for substitution reactions. Addition of phenylboronic acids to *meso*-diacetate **15** gives **16a** bearing two stereogenic centres and an *exo*-cyclic alkene – effectively a remote substitution process on a non-conjugated homo-allylic acetate. We propose these reactions occur *via* a carbometallation, β -hydride elimination, hydorrhodation and β -oxygen elimination sequence to form **16** (Fig. 4d). A base is required to achieve high conversion – likely for the regeneration of active Rh-hydroxide complex **I**. The reaction tolerates several electron-rich arylboronic acid coupling partners (Table 4, **16a-16j**).

For electron-deficient arylboronic acids, we observed a reductive Heck reaction as the major pathway (Table 4, **17a-16c**). Here, the hydroarylation arises from C–H insertion processes (which are faster for electron-deficient boronic acids) and subsequent protonation (Fig. 4d)^{29,42}. This alternative pathway gives diminished yields for the remote substitution products **16e**, **16g** and **16h**, and in these cases we isolated significant amounts of the reductive Heck product (Table 4).

The chemodivergence of this process is both dependent on the electronic nature of the boronic acid and the ligand. For instance, with (*S*)-DTBM-Segphos we obtained the hydroarylation product **17n** as the major product, and changing the ligand to (*S*)-Segphos gives access to the remote substitution product **16n** instead (Fig. 4e). Alternative leaving groups including a dicarbonate and diphosphate also gave good results (Table 4, **16aa-16ba**).

Conclusion

We have demonstrated that catalytic asymmetric carbometallation processes are possible with cyclobutenes – despite the relatively low gain in strain relief compared to established carbometallations with cyclopropenes and bicyclic species. As the carbometallation step does not require any activating or directing groups, a wide variety of substituted cyclobutenes were found to undergo this transformation. The metallated cyclobutenes can then follow different pathways, including C–H activation and chain-walking, in order to achieve protonation or elimination and to regenerate the catalyst. These reactions include unusual 1,5-addition processes and homo-allylic arylation on non-conjugated olefins and provide a wide range of enantiomerically enriched complex cyclobutanes. This procedure is expected to be directly used in biomedical and agrochemical research and the fine chemicals industry. We anticipate that other transition metal catalysed cyclobutene carbometallation processes with alternative nucleophiles are possible, and their investigation is likely to uncover additional new and useful reactivity patterns.

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Figures

Fig. 1 | Catalytic cross-coupling towards complex, chiral cyclobutanes. **a**, Representative stereochemically complex, biologically active cyclobutanes. **b**, Our approach: Rhodium-catalysed arylation of diverse cyclobutenes. Asymmetric carbometallation gives a common cyclobutyl rhodium intermediate which can undergo chain-walking or C–H insertion. Protonation or elimination can then serve as terminating mechanisms and thus enable reductive Heck, 1,5-addition and remote substitution reactivity. X = NR, SO₂, C=O, OR; Y = OR.

Fig. 2 | Proposed reaction mechanism. **a**, Catalytic cycle based on deuterium-labelling and side-products. After transmetallation of the boronic acid to Rh-catalyst **I**, enantioselective carbometallation of cyclobutene **1** gives a cyclobutyl-rhodium complex **III**. **III** can then undergo a chain-walking process followed by protonation to give the product **3a**, or a C–H insertion process followed by a second cyclobutene addition to give dimeric **3a'**. **b**, Chain-walking process. Reversible β -hydride elimination and 1,2-hydride shifts result in deuterium-incorporation at the C(2) position.

Fig. 3 | Asymmetric 1,5-additions triggered by carbometallation. **a**, Formation of a rhodium oxa- π -allyl complex *via* chain-walking. Complex **XI** serves as thermodynamic sink and as protonation site as shown by deuterium labelling. **b**, Hydroarylation of monocyclic cyclobutenes takes advantage of the formation of a rhodium oxa- π -allyl complex and gives access to the *trans-trans* product (Isolated

yield of the major diastereomer). **c**, Regiodivergent reaction on a racemic mixture. Each enantiomer of the racemic starting material gives a different, separable regioisomeric product. **d**, Formal syntheses of Belaperidone *via* two catalytic asymmetric addition reactions.

^a LiAlH₄, Et₂O/CH₂Cl₂, 23 °C, 16 h.

^b CbzCl, toluene, 80 °C, 1.5 h, 84 % (over two steps).

^c See Table 1, 45%, 97% e.e..

^d H₂, Pd(OH)₂/C, MeOH, 23 °C, 5 h, 94%.

^e [Rh(cod)OH]₂ (0.5 mol%), (*S*)-DTBM-Segphos (1.2 mol%), 4-FPhB(OH)₂ in toluene/dioxane/H₂O (5:5:1, 0.5 M), 60 °C, 16 h, 72%, 98% e.e..

^f LiAlH₄, Et₂O/CH₂Cl₂, 23 °C, 16 h, 89%.

^g H₂, Pd(OH)₂/C, MeOH, 23 °C, 16 h, 99%.

^h For conversion of amine **10** to Belaperidone (**11**) see ref.³⁸.

Fig. 4 | Reductive Heck reactions and remote substitution. **a**, Formal synthesis of PF-04862853 *via* a regioselective arylation. **b**, Mechanism for regioselective reductive Heck. A chiral intermediate **XIII** is formed *via* carborhodation. The chirality is lost in the C–H insertion step and deuterium-incorporation occurs at the C(2') position. **c**, Diastereo- and regioselective reductive Heck with a racemic, spirocyclic cyclobutene. **d**, Mechanism for divergence in remote Substitution and hydroarylation. After initial carborhodation, **XV** can either undergo chain-walking and subsequent β-oxygen elimination to give the remote substitution product **16**. Alternatively, C–H insertion process followed by protonation gives **17**. **e**, Ligand induced switching of chemoselectivity. The selectivity of this process is dependent on the electronics of the boronic acid and the ligand.

^a [Rh(cod)OH]₂ (5.0 mol%), dppe (12.0 mol%), cyclobutene (0.4 mmol), 3-Cl,4-FPhB(OH)₂ (1.2 mmol), aq. CsOH (0.4 mmol) in toluene/dioxane/H₂O (4.5: 4.5:1, 0.1 M) at 60 °C for 16 h.

^b For conversion of protected amine **13k** to PF-04862853 (**14**) see ref.⁴¹.

^c [Rh(cod)OH]₂ (2.5 mol%), (*S*)-DTBM-Segphos (6.0 mol%), cyclobutene (0.4 mmol), 4-CF₃PhB(OH)₂ (0.8 mmol), Cs₂CO₃ (0.4 mmol) in toluene/dioxane/H₂O (25:25:1, 0.1 M) at room temperature (23 °C), 16 h.

^d Standard conditions as in ^c with (*S*)-Segphos instead of (*S*)-DTBM-Segphos.

Tables

Table 1 | Hydroarylation of bicyclic cyclobutenes *via* remote protonation of alkyl rhodium complexes

Conditions: all reactions were carried out with [Rh(cod)OH]₂ (2.5 mol%), (*S*)-Segphos (6.0 mol%), cyclobutene (0.4 mmol) and boronic acid (0.8 mmol) in toluene/dioxane/H₂O (25:25:1, 0.1 M) at room temperature (23 °C) for 16 h. Enantiomeric excess (e.e.) values were determined by SFC analysis on a chiral non-racemic stationary phase.

^a Performed at 60 °C.

^b (*S*)-BINAP instead of (*S*)-Segphos.

^c (*S*)-DTBM-Segphos instead of (*S*)-Segphos.

^d 3 equiv. of boronic acid.

Boc, *N*-tert-butoxycarbonyl; cod, 1,5-cyclooctadiene; Cbz, carboxybenzyl; Ts, 4-toluenesulfonyl.

Table 2 | Asymmetric 1,5-addition to a non-conjugated β,γ-unsaturated carbonyl compound

Conditions: all reactions were carried out with [Rh(cod)OH]₂ (2.5 mol%), (*S*)-Segphos (6.0 mol%), cyclobutene (0.4 mmol) and boronic acid (0.8 - 1.2 mmol) in toluene/dioxane/H₂O (25:25:1, 0.1 M) at 60 °C for 4 h. Enantiomeric excess (e.e.) values were determined by SFC analysis on a chiral non-racemic stationary phase.

Table 3 | Regioselective reductive Heck reactions with a spirocyclic, prochiral cyclobutene

Conditions: all reactions were carried out with [Rh(cod)OH]₂ (2.5 mol%), dppe (6.0 mol%), cyclobutene (0.4 mmol), boronic acid (1.2 mmol), aq. CsOH (0.4 mmol) in toluene/dioxane/H₂O (4.5: 4.5:1, 0.1 M) at 60 °C for 16 h.

Table 4 | Remote substitution

Conditions: all reactions were carried out with [Rh(cod)OH]₂ (2.5 mol%), (*S*)-DTBM-Segphos (6.0 mol%), cyclobutene (0.4 mmol), boronic acid (0.8 - 1.2 mmol), Cs₂CO₃ (0.4 mmol) in toluene/dioxane/H₂O (25:25:1, 0.1 M) at room temperature (23 °C) for 16 h. Enantiomeric excess (e.e.) values were determined by SFC analysis on a chiral non-racemic stationary phase.

^a Performed at 60 °C.

Methods

General procedure for the cross-coupling of arylboronic acids and cyclobutenes

All reactions were carried out under an inert argon atmosphere using standard Schlenk techniques with all reagents weighed open to air.

Preparation of the catalyst. A stock solution of the rhodium hydroxy phosphine complex was prepared by stirring a solution of $[\text{Rh}(\text{cod})\text{OH}]_2$ (20.5 mg, 0.045 mmol, 2.5 mol%) and bidentate phosphine ligand (0.108 mmol, 6.0 mol%) in dry dioxane (9.0 mL) under an argon atmosphere at 60 °C for 30 min. When the addition reaction was performed at room temperature (23 °C), the rhodium hydroxy phosphine complex was allowed to reach room temperature (23 °C) over 5–10 min. (This solution was used for four cross-coupling reactions on 0.4 mmol scale and was always used within the next 15 min.)

Cross-coupling. A portion of the resulting orange-red solution (2.0 mL; 0.05 equiv. $[\text{Rh}]$) was added to a 10 mL round-bottom flask containing a mixture of boronic acid (0.80 - 1.20 mmol, 2.0 – 3.0 equiv.) and cyclobutene (0.40 mmol, 1.0 equiv.) in toluene (2 mL) and H_2O (0.080 mL) *via* syringe under an argon atmosphere. The resulting mixture was then stirred at room temperature (23 °C) or 60 °C for a specified time. The mixture was diluted with hexane (1 mL) and concentrated *in vacuo*. The crude mixture was directly loaded on a silica gel flash column and eluted with the indicated solvent mixture to afford the desired product.

All modifications from this procedure are specified within the Supplementary Information of the Article.

Data availability

All data (experimental procedures and characterization data) supporting the findings of this study are available within the Article and its Supplementary Information.