Rhodium-Catalyzed Asymmetric Allylic Arylation of Racemic Halides with Arylboronic Acids

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C_{sp2}-C_{sp2} cross-coupling reactions between arylboronic acid and aryl halides are widely used in both academia and industry and are strategically important in the development of new agrochemicals and pharmaceuticals. Less well-developed are C_{sp2}-C_{sp3} cross-coupling reactions being its enantioselective version very rare. Here we report a highly enantioselective C_{sp2}-C_{sp3} bond forming method that couples arylboronic acids to racemic allyl chlorides. Both enantiomers of a cyclic chloride are converted into a single enantiomer of product via a dynamic kinetic asymmetric transformation (DYKAT). This rhodium-catalyzed method uses readily available and inexpensive building blocks and is fast, mild and broadly applicable. In the case of electron deficient, electron rich or *ortho*-substituted boronic acids better results are obtained with racemic allyl bromides. Oxygen-substitution in the allyl halide is tolerated and the reaction products can be readily functionalized to provide diverse building blocks, filling a significant gap in methods for catalytic asymmetric synthesis.

One of the most widely used approaches to carbon-carbon bond formation in the fine chemical, pharmaceutical, and agrochemical industries, as well as in the synthesis of organic materials, is sp^2-sp^2 cross-coupling[1]. In particular the Suzuki-Miyaura reaction (Fig. 1A) is robust, convenient and widely used in the synthesis of lead compounds for the development of new medicines as it is well-suited to producing libraries of compounds[2–4]. The Suzuki-Miyaura reaction uses arylboronic acid reagents, which are relatively air-stable and readily available[5]. The generally favorable reactivity profile and high atom economy of boronic acids makes them highly desirable reaction partners in synthetic and medicinal chemistry[6], particularly when compared to alternative sp^2-hybridized organometallic reagents used in C-C bond forming reactions[7].

The development of robust and widely applicable methods that form single enantiomer products is a major contemporary research goal[8]. Hayashi developed rhodium-catalyzed asymmetric conjugate addition reactions of boronic acid nucleophiles to prochiral α,β-unsaturated ketones with excellent yield and enantioselectivity[9,10] (Fig. 1B) and many related protocols have since been developed[11]. Rh-catalyzed allylic substitutions have unique features and can be highly regioselective[12]. Evans reported that alkylations with stabilized nucleophiles[13,14] and arylations with non-stabilized aryl zinc nucleophiles[15] are highly stereospecific processes; overall retention of configuration is observed using stabilized nucleophiles and overall inversion occurs with arylzinc compounds, so that highly enantiomerically enriched compounds can be obtained by starting from single enantiomer allylic coupling partners (Fig. 1C). There are only limited examples of rhodium-catalyzed asymmetric allylic substitutions: Rh-catalyzed asymmetric allylic alkylation employing stabilized nucleophiles was reported in 2003[16] and Lautens and co-workers reported the asymmetric addition of arylboronic acids to prochiral *meso*-allylic diol derivatives[17,18] and *meso*-bicyclic alkenes[19].

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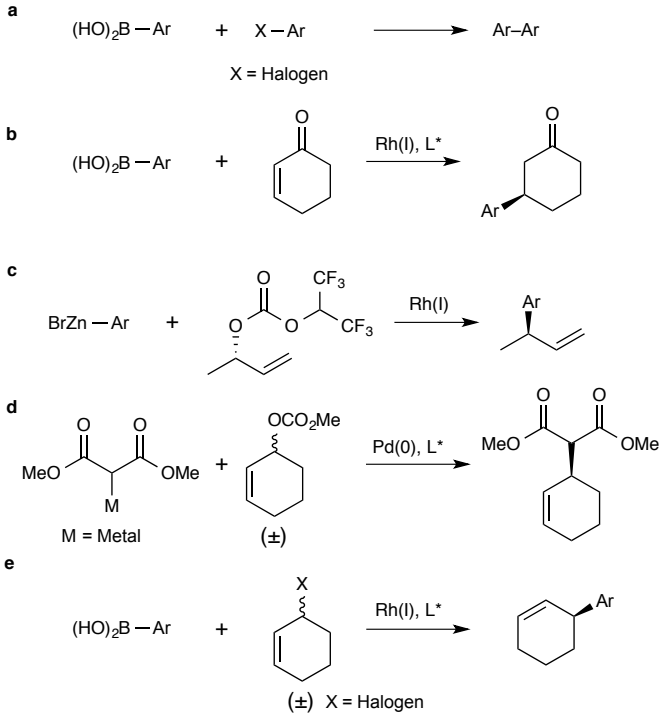


Figure 1. C-C bond forming reactions and this work. (**a**) Suzuki–Miyaura cross-coupling to form a C_{sp2}-C_{sp2} bond. (**b**) Rh(I)-catalyzed asymmetric conjugate addition of boronic acids to prochiral enones. (**c**) Enantiospecific allylic arylation using an sp^2-hybridized aryl nucleophile and a single enantiomer allyl carbonate. (**d**) Pd-catalyzed DYKAT using stabilized nucleophiles and racemic allylic coupling partners to form single enantiomer compounds containing a new C_{sp3}-C_{sp3} bond. (**e**) This work: the Rh-catalyzed asymmetric allylic arylation of racemic halides with arylboronic acids allows the formation of single enantiomer compounds containing a new C_{sp3}-C_{sp2} bond avoiding the use of stabilized nucleophiles.

The relative lack of Rh-catalyzed allylic substitution methods is remarkable. Metal-catalyzed asymmetric allylic alkylation (AAA) reactions are very widely used[20,21], but the unique stereoselectivity issues described above appear to have conspired to make comparable Rh-catalyzed processes difficult. A particularly powerful class of AAA reactions allow the conversion of *racemic* starting materials into single enantiomer products[22,23] rather than starting from *single enantiomer* or *prochiral* starting materials. Pd-catalyzed processes that convert a racemic mixture of starting materials into a new single enantiomer product are commonly referred to as *dynamic kinetic asymmetric transformations* (DYKATs) as originally developed by Trost. DYKATs can now be used with a wide variety of stabilized nucleophiles and an array of metal catalysts[24] and several non-stabilized sp^3-hybridized nucleophiles can now be used in certain related procedures[25–28].

We recently reported Cu-catalyzed DYKATs where sp^3-hybridized alkylzirconium nucleophiles add to racemic cyclic allyl chlorides[29]. Preliminary mechanistic studies suggest that a rapidly isomerizing allyl halide intermediate serves to racemize the substrate, which allows the formation of single enantiomer products with isolated yields of >50%. Our attempts to extend this method to sp^2-hybridized alkenylzirconium nucleophiles proved difficult; only modest enantioselectivity was observed at cryogenic temperatures and the reaction was very limited in scope[30]. To the best of our knowledge only one example of DYKAT using sp^2-hybridized nucleophiles has been reported.[31]

Results and discussion

We decided to examine the use of aryl boronic acids in rhodium-catalyzed DYKATs, considering that that enantioselective addition of sp^2-hybridized nucleophiles to racemic starting materials may overcome the difficulties described above that have limited the development of Rh-catalyzed AAA reactions. Further, while asymmetric Suzuki-Miyaura coupling to form axially chiral C_{sp2}-C_{sp2} biaryl bonds is now reasonably well developed,[32,33] Rh-catalyzed DYKATs would provide a straightforward asymmetric coupling method to form new C_{sp2}-C_{sp3} bonds. There is a long-standing need for robust and reliable C-C bond forming methods suitable for diversifying the compounds synthesized in medicinal chemistry and drug discovery programmes.[2–4,34,35]

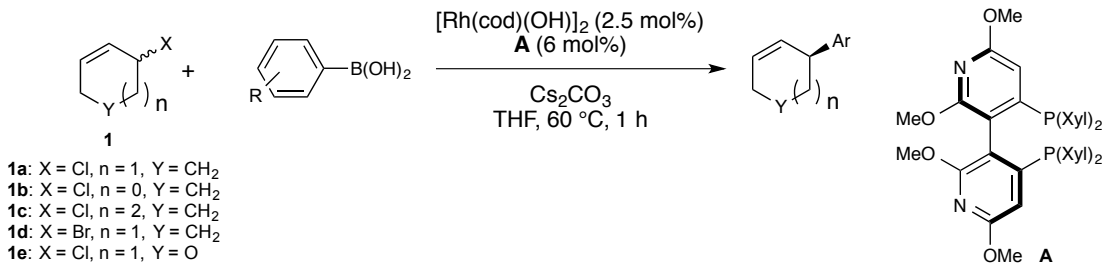
We began by exploring the arylation of racemic 3-chlorocyclohex-1-ene **1** with phenylboronic acid under a set of Hayashi conditions[36] using 10 mol% $Rh(acac)(C_2H_4)_2$, and 12 mol% (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) in dioxane-H_2O at 100 °C. 3-chlorocyclohexene **1** completely decomposed under these conditions, presumably because of its sensitivity to nucleophilic attack by water. Changing the solvent to THF, adding a base such as Cs_2CO_3 and heating at 60 °C also gave no product after several hours. We then explored other rhodium sources. The acetylacetone (acac) ligand is known to strongly bind to Rh and slow down transmetallation, which could be detrimental to catalyst activity[37]. The $[Rh(cod)(OH)]_2$ salt combined with (*S*)-BINAP gave the desired coupling product, but in very low yield. Ligand structure proved to be crucial to the outcome of the reaction, and ultimately (*S*)-Xyl-P-PHOS **A**, which has previously been used in a very similar combination by Lautens,[18] proved to be highly efficient, and give **2** in quantitative yield with excellent enantioselectivity (99%) after 1 hour at 60 ºC (Table 1, entry 1).

The scope of the reaction using racemic allyl chlorides and ligand **A** was explored using the following conditions: 2.5 mol% of $[Rh(cod)(OH)]_2$, 6 mol% of ligand **A**, 1.0 equivalent of Cs_2CO_3 in THF at 60 °C for one hour. Using simple arylboronic acids, the products were obtained with good yields and excellent enantioselectivities (Table 1, entries 2 and 3). The functional group tolerance was explored. Electron-donating groups such as methyl- and methoxy- in the *para*-position of the arylboronic acid (entries 4 and 5) gave slightly lower yields but excellent enantioselectivities. A trifluoromethyl group in the *para*-position also gave high enantioselectivity (entry 6), as did an electron withdrawing *meta*-CO_2Me group (entry 7). The reaction proceeded smoothly even when the aromatic ring bore halogen substituents (entries 8 to 11). Using phenylboronic acid, we examined racemic five- (n = 0, entry 12) and seven- (n = 2, entry 13) membered ring allyl chlorides. In these cases longer reaction times were required (4 h) to obtain good yields enantioselectivity (>99% ee and 97% ee respectively).

When more challenging boronic acids were explored, a number of them performed poorly using the above conditions. However, we found that using commercially available racemic allyl bromide **1d** rather than **1a** gave good yields and high enantioselectivities (entries 14 to 19). For example, a sterically hindered *ortho*-methyl-phenylboronic acid did not give product using the chloride **1a**, but **15** was easily produced in 1 hour at 60 ºC using **1d**. Substitution that would be expected to strongly influence the electron density of the nucleophile, such as 3-nitro, 2-methoxy, or 2,4-difluoro-phenylboronic acids (to give **16**, **17**, and **18** respectively) did not give

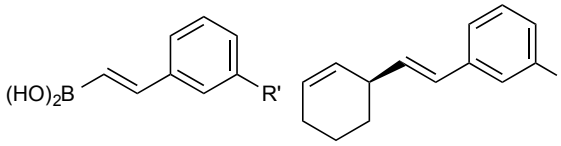
desired product when using 3-chlorocyclohex-1-ene **1a**, but use of the bromide **1d** again overcame this problem allowing these challenging nucleophiles to undergo asymmetric arylation with good to excellent enantioselectivity (74-96% ee, entries15-17). Phenolic boronic acids also perform well in combination with the allylic bromide to give **19** and **20**, if the OH-group is suitably protected.

Table 1. Reaction Scope.



1a: X = Cl, n = 1, Y = CH_2
1b: X = Cl, n = 0, Y = CH_2
1c: X = Cl, n = 2, Y = CH_2
1d: X = Br, n = 1, Y = CH_2
1e: X = Cl, n = 1, Y = O

Entry	1	Aryl Boronic Acid	Product	Yield[a]	ee[b]
1	**1a**	R = H	**2**, R = H	99%	99%
2		Ar = 2-Naph	**3**, Ar = 2-Naph	96%	89%
3		R = 3-Me	**4**, R = 3-Me	96%	97%
4		R = 4-Me	**5**, R = 4-Me	58%	>94%
5		R = 4-OMe	**6**, R = 4-OMe	77%	97%
6		R = 4-CF_3	**7**, R = 4-CF_3	60%	96%
7		R = 3-CO_2Me	**8**, R = 3-CO_2Me	86%	>99%
8		R = 4-F	**9**, R = 4-F	54%	>99%
9		R = 4-Cl	**10**, R = 4-Cl	81%	>99%
10		R = 3-Cl	**11**, R = 3-Cl	70%	99%
11		R = 3-Br	**12**, R = 3-Br	56%	96%
12[c]	**1b**	R = H	**13**	67%	>99%
13[c]	**1c**	R = H	**14**	62%	97%
14	**1d**	R = 2-Me	**15**, R = 2-Me	45%	>99%
15		R = 3-NO_2	**16**, R = 3-NO_2	51%	96%
16		R = 2-OMe	**17**, R = 2-OMe	80%	74%
17		R = 2,4-difluoro	**18**, R = 2,4-difluoro	53%	92%
18		R = 4-OBn	**19**, R = 4-OBn	61%	84%
19		R = 4-OTBS	**20,** R = 4-OTBS	40%	99%
20	**1e**	R = H	**21**, R = H	99%	96%
21		Ar = 2-Naph	**22**, Ar = 2-Naph	90%	98%
22		R = 3-Me	**23**, R = 3-Me	99%	>99%
23		R = 4-Cl	**24**, R = 4-Cl	83%	99%

24	R = 4-OMe		**25**, R = 4-OMe	81%	>99%
25	**1a**		**26**, R′ = H	67%	96%
26			**27**,R′ = 3-Me	52%	94%
27			**28**, R′ = 3-F	44%	92%

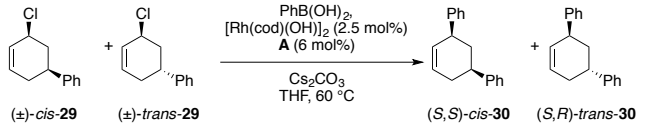
Conditions: Boronic acid (2.5 eq), vinyl halide (1.0 eq), $[Rh(cod)(OH)]_2$ (2.5 mol%), Ligand **A** (6 mol%). [a] Isolated yield. [b] Absolute configurations known or assigned by analogy (see Supplementary Information). [c] Stirring 4 h at 60 °C protected from light.

We reasoned that it would be useful to be able to perform asymmetric allylic arylations with heterocyclic racemic acceptors. The products of these reactions feature different organic skeletons and could be further functionalized. We examined use of 3-chloro-3,6-dihydro-2*H*-pyran **1e** as a proof of concept. Pleasingly, the same conditions used above gave highly enantioselective reactions, which suggest that these reactions are robust and may be widely applicable. Using five different arylboronic acids (entries 20-24) the reaction proceeded smoothly to give uniformly high yields and enantioselectivities (all >96% ee) with no further optimization of the reaction conditions (**21**-**25**).

We also found that vinylboronic acids can also be used as nucleophiles under the same reaction conditions (entries 25-27). Here, good yields and high levels of enantioselectivity were observed when the reaction time was extended from 1 h to 4 h (**26**–**28**).

Understanding the mechanism of asymmetric arylation in these DYKATs is key to extending and improving the methods further. In Pd-catalyzed AAAs with stabilized nucleophiles, asymmetric induction is determined during attack of the nucleophile onto a carbon atom of a π-allyl-Pd intermediate[20]. However, non-stabilized nucleophiles react at the metal centre first[38] – so a different mechanistic pathway is working here. Previously reported Rh-catalyzed allylic substitutions are highly stereospecific, with net inversion observed using non-stabilized arylzinc nucleophiles.[15] In the case of Rh(I)-catalyzed addition of arylboronic acids, ligand controlled S_N2 or S_N2' allylic displacement – both with overall inversion, are observed in asymmetric desymmetrization processes.[18] Establishing the stereochemical outcome is more complicated here since the starting material is racemic and the preparation of enantiopure or even enantioenriched **1** would be really difficult. It is possible that under the reaction conditions (heating in THF) the halide anion co-product scrambles the configuration of the remaining starting material[29] and obscures attempts to gain mechanistic insight. To shed light on the regiochemical outcome of these DYKATs we examined the AAA of 3-chloro-5-phenylcyclohex-1-ene **29** with phenylboronic acid (Table 2).

Table 2. Stereoselectivity of allylic arylation.



(±)-*cis*-**29** (±)-*trans*-**29** (*S*,*S*)-*cis*-**30** (*S*,*R*)-*trans*-**30**

Entry	29 cis:trans[a]	Conversion (%)	Remaining 29 cis:trans[a]	30 cis:trans[a]	*cis*-30 ee[b] (%)	*trans*-30 ee[b] (%)
1	1:25	100	–	25:1	99.4	98
2	1:5.3	100	–	5.3:1	99.2	99.2
3	6.1:1	100	–	1:5.3	98	99.1
4[c]	6.1:1	84	>50:1	1:4.5	97	99.1

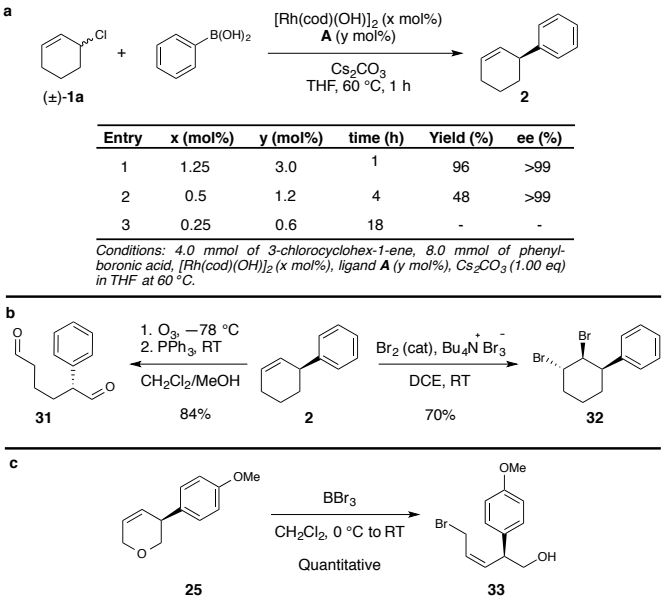
Conditions: 1.0 eq of 3-chlorocyclohex-1-ene, 2.0 eq of benzeneboronic acid, $[Rh(cod)(OH)]_2$ (2.5 mol%), ligand ***A*** *(6 mol%), Cs_2CO_3 (1.00 eq) in THF at 60 °C stirring 18 h.*
[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by chiral HPLC. [c] Reaction stopped after 3 h.

Different *cis*- and *trans*- ratios of *racemic* **29** were prepared and subjected to the reaction conditions. These experiments clearly show that DYKAT occurs with *overall inversion* of configuration. When using a *cis*:*trans* ratio of 1:25 starting material **29** was converted into **30** (100% conversion, 96% isolated yield) with a *cis*:*trans* ratio of 25:1 (Fig 2, Table 1, entry 1), where the relative stereochemistry of the starting material and product have been completely inverted and *cis*-**30** and *trans*-**30** were obtained with >98% ee. When a different starting *cis*:*trans* ratio of **29** is used (1:5.3), **30** was again obtained with complete relative inversion (Entry 2; a 5.3:1 ratio in favour of the *cis*-biaryl product, both products 99.2% ee).

Entry 3 shows that when a ratio of **29** in favor of the *cis*-isomer (*cis*:*trans* = 6.1:1) was used, **30** was obtained as a 1:5.3 *cis*:*trans* ratio, so that enantioselective (both diastereomers >98% ee) inversion of configuration was again observed, but some loss of diastereomeric integrity occurred. Further insight was gained by using the same 6.1:1 *cis*:*trans* ratio of **29**, but stopping the reaction after 3 h (Entry 4). Here, the reaction conversion was 84% and the remaining 16% of starting material was as a ~52:1 ratio of *cis*:*trans*, suggesting that *trans*-**29** reacts faster than *cis*-**29** under the reaction conditions. Here, **30** was obtained as a mixture of diastereoisomers with a 1:4.5 *cis*:*trans* ratio and we note that reaction of the remaining starting material would be expected to increase the ratio of **30** to that seen in Entry 3. In both experiments (Entries 3 and 4) with a starting excess of *cis*-**29**, we observe erosion of the diastereomeric ratio, and we speculate that this is due to partial isomerization of the starting material from *cis*-**29** to *trans*-**29** during the reaction.

These observations suggest that both racemic isomers undergo *overall enantioselective inversion* processes to give the respective isomers of product **30**. We provisionally assign the absolute configuration of both *cis*- and *trans*-**30** by analogy to the asymmetric reaction with unsubstituted allyl halides, so that ligand (*S*)-**A** would favour the formation of the (*S*,*S*)-3,5-disubstituted cyclohexene derivative. We find that the observed enantioselectivity in both *cis*- and *trans*-**30** is practically identical and uniformly high is quite remarkable. We also examined the relationship between the enantiomeric excess of product **2** and the enantiomeric excess of catalyst **A** in the coupling (±)-**1a** and phenylboronic acid. There exists a very good linear relationship, suggesting that the active species in the catalytic cycle is a monomeric Rh(I)-ligand complex (See Supplementary Information, Fig. S1)[39]. While it is clear that these reactions are capable of highly enantioselective conversions of both enantiomers of a starting material into a single enantiomer of product with overall inversion of

configuration, elucidating the full details of these transformations will require further studies.



Entry	x (mol%)	y (mol%)	time (h)	Yield (%)	ee (%)
1	1.25	3.0	1	96	>99
2	0.5	1.2	4	48	>99
3	0.25	0.6	18	-	-

*Conditions: 4.0 mmol of 3-chlorocyclohex-1-ene, 8.0 mmol of phenylboronic acid, $[Rh(cod)(OH)]_2$ (x mol%), ligand **A** (y mol%), Cs_2CO_3 (1.00 eq) in THF at 60 °C.*

Figure 2. (**a**) Scale-up experiments allowed the preparation of more than 600 mg of **2** and the catalyst loading was lowered down to 1 mol% of Rh(I). (**b**) Transformations of alkene **2** to synthetically valuable building blocks. (**c**) Regioselective boron tribromide mediated ring opening of a 3,6-dihydro-2*H*-pyran derivative to give a highly functionalized product that offers a variety of possibilities for further transformations.

The above reaction conditions use 5 mol% Rh and 6 mol% of ligand **A**. We briefly examined experiments to determine if the reaction could be scaled-up and if the catalyst loading could be lowered (Fig. 2a). Using the standard conditions on a 4.0 mmol scale, more than 600 mg of **2** can be prepared with no fine-tuning of the reaction conditions. Dropping the catalyst loading to 1.25 mol% of $[Rh(cod)(OH)]_2$ (which is a total of 2.5 mol% Rh) and 3 mol% of ligand **A**, gave **2** with comparable yield and enantioselectivity (Table 1, entry 1; 96%, 99.1% ee). When we decreased the catalyst loading to 0.5 mol% of $[Rh(cod)(OH)]_2$ and 1.2 mol% of ligand **A** there was no loss of enantioselectivity (99.7% ee) but lower yield (48%) was obtained after 4 h even though the reaction was complete (Entry 2). Reducing the catalyst loading to 0.25 mol% of $[Rh(cod)(OH)]_2$, completely inhibited the reaction (Entry 3) even at extended (18 h) reaction times. Using the same catalyst loading (0.25 mol%) at 4 times the concentration (0.4 M) also gave no product (not shown).

Finally, we aimed to demonstrate that this method could be used to prepare diverse building blocks for synthesis. When **2** was subjected to ozonolysis, dialdehyde **31** was obtained in very good yield (84%) in 30 min (Fig. 4B). Dibromination of alkene **2** was found to exclusively produce a single isolable diastereomer of product ((1*R*,2*S*,3*S*)-2,3-dibromocyclohexyl)benzene **32** (70%) when using 1.5 equiv. of tetrabutylammonium tribromide in combination with catalytic Br_2 in dichloroethane (Fig. 4B). We also demonstrate that it is possible to selectively cleave the heterocyclic ring in the 2*H*-pyran derivatives obtained by our method; **25** can be regioselectively opened using BBr_3 in dichloromethane to produce (*S*,*Z*)-5-bromo-2-(4-methoxyphenyl)pent-3-en-1-ol **33** quantitatively (Fig. 4C).

Conclusions

To summarize, we have developed a novel dynamic kinetic asymmetric allylic arylation of *racemic* allylic halides using boronic acid nucleophiles and rhodium catalysts. The mild and robust reaction conditions are smooth, allow the use of a variety of different nucleophiles and electrophiles and the reaction can be easily scaled up to 4.0 mmol while decreasing the catalyst loading to 1 mol% rhodium. It is anticipated that this reaction will serve as the basis for the development of a broadly useful asymmetric variant of Suzuki-Miyaura coupling and that this approach will eventually allow the preparation of a wide variety of versatile building blocks for synthesis, medicinal and materials chemistry.

Methods

General procedure for the asymmetric allylic alkylation of allyl chlorides with boronic acids: In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (S)-Xyl-P-PHOS **A** (18.2 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2 mL) at 60 °C for 30 min. A solution of the boronic acid (0.80 mmol, 2.00 eq) and the allyl chloride (0.40 mmol, 1.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with THF (0.5 mL). The resulting mixture was then stirred for 1 h at 60 °C before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded onto a flash chromatography column to obtain the purified product.

Materials and methods, all procedures, characterization data and spectra are available in the Supplementary Information.

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Author contributions

M.S. performed the experiments. S.F. guided the research. Both authors contributed to designing the experiments, analysing the data and writing the manuscript.

Additional information

Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to S.F.

References

1. Armin de Meijere, Stefan Brase, M. O. *Metal Catalyzed Cross-Coupling Reactions and More*. (Wiley-VCH, Weinheim, 2014).

2. Cooper, T. W. J., Campbell, I. B. & MacDonald, S. J. F. Factors determining the selection of organic reactions by medicinal chemists and the use of these reactions in arrays (Small Focused Libraries). *Angew. Chem. Int. Ed.* **49,** 8082–8091 (2010).

3. Nadin, A., Hattotuwagama, C. & Churcher, I. Lead-oriented synthesis: A new opportunity for synthetic chemistry. *Angew. Chem. Int. Ed.* **51,** 1114–1122 (2012).

4. Roughley, S. D. & Jordan, A. M. The medicinal chemist's toolbox: An analysis of reactions used in the pursuit of drug candidates. *J. Med. Chem.* **54,** 3451–3479 (2011).

5. Lennox, A. J. J. & Lloyd-Jones, G. C. Selection of boron reagents for Suzuki-Miyaura coupling. *Chem. Soc. Rev.* **43,** 412–443 (2014).

6. Hall, D. G. *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*. *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine* (Wiley-VCH, Weinheim, 2006).

7. Howell, G. P. Asymmetric and Diastereoselective Conjugate Addition Reactions: C–C Bond Formation at Large Scale. *Org. Process Res. Dev.* **16,** 1258–1272 (2012).

8. Jacobsen, E. N., Pfaltz, A. & Yamamoto, H. *Comprehensive Asymmetric Catalysis: Suppl. 2*. (Springer, 2004).

9. Takaya, Y., Ogasawara, M. & Hayashi, T. Rhodium-Catalyzed Asymmetric 1 , 4-Addition of Aryl- and Alkenylboronic Acids to Enones. *J. Am. Chem. Soc.* **3,** 5579–5580 (1998).

10. Hayashi, T. & Yamasaki, K. Rhodium-catalyzed asymmetric 1,4-addition and its related asymmetric reactions. *Chem. Rev.* **103,** 2829–2844 (2003).

11. Evans, P. A. *Modern Rhodium-Catalyzed Organic Reactions*. *Modern Rhodium-Catalyzed Organic Reactions* (Wiley-VCH, 2005).

12. Tsuji, J., Minami, I. & Shimizu, I. Allyation of carbonucleophiles with allylic carbonates under neutral conditions catalyzed by rhodium complexes. *Tetrahedron Lett.* **25,** 5157–5160 (1984).

13. Evans, P. a & Kennedy, L. J. Enantiospecific and regioselective rhodium-catalyzed allylic alkylation: diastereoselective approach to quaternary carbon stereogenic centers. *Org. Lett.* **2,** 2213–2215 (2000).

14. Evans, P. A. & Leahy, D. K. Regioselective and enantiospecific rhodium-catalyzed allylic alkylation reactions using copper(I) enolates: Synthesis of (–)-sugiresinol dimethyl ether. *J. Am. Chem. Soc.* **125,** 8974–8975 (2003).

15. Evans, P. A. & Uraguchi, D. Regio- and enantiospecific rhodium-catalyzed arylation of unsymmetrical fluorinated acyclic allylic carbonates: inversion of absolute configuration. *J. Am. Chem. Soc.* **125,** 7158–7159 (2003).

16. Hayashi, T., Okada, A., Suzuka, T. & Kawatsura, M. High enantioselectivity in rhodium-catalyzed allylic alkylation of 1-substituted 2-propenyl acetates. *Org. Lett.* **5,** 1713–1715 (2003).

17. Menard, F., Chapman, T. M., Dockendorff, C. & Lautens, M. Rhodium-catalyzed asymmetric allylic substitution with boronic acid nucleophiles. *Org. Lett.* **8,** 4569–4572 (2006).

18. Menard, F., Perez, D., Sustac Roman, D., Chapman, T. M. & Lautens, M. Ligand-controlled selectivity in the desymmetrization of meso cyclopenten-1,4-diols via rhodium(I)-catalyzed addition of arylboronic acids. *J. Org. Chem.* **75,** 4056–4068 (2010).

19. Lautens, M., Fagnou, K. & Hiebert, S. Transition metal-catalyzed enantioselective ring-opening reactions of oxabicyclic alkenes. *Acc. Chem. Res.* **36,** 48–58 (2003).

20. Trost, B. M. & Van Vranken, D. L. Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev.* **96,** 395–422 (1996).

21. Lu, Z. & Ma, S. Metal-catalyzed enantioselective allylation in asymmetric synthesis. *Angew. Chem. Int. Ed.* **47,** 258–297 (2008).

22. Huerta, F. F., Minidis, A. B. E. & Bäckvall, J. Racemisation in asymmetric synthesis . Dynamic kinetic resolution and related processes in enzyme and metal catalysis. *Chem. Soc. Rev.* **30,** 321–331 (2001).

23. Vedejs, E. & Jure, M. Efficiency in nonenzymatic kinetic resolution. *Angew. Chem. Int. Ed.* **44,** 3974–4001 (2005).

24. Trost, Barry M., Fandrick, D. R. Palladium-catalyzed dynamic kinetic asymmetric allylic alkylation with the DPPBA ligands. *Aldrichimica Acta* **40,** 59–72 (2007).

25. Trost, B. M. & Thaisrivongs, D. a. Strategy for employing unstabilized nucleophiles in palladium-catalyzed asymmetric allylic alkylations. *J. Am. Chem. Soc.* **130,** 14092–14093 (2008).

26. Misale, A., Niyomchon, S., Luparia, M. & Maulide, N. Asymmetric palladium-catalyzed allylic alkylation using dialkylzinc reagents: a remarkable ligand effect. *Angew. Chem. Int. Ed.* **53,** 7068–7073 (2014).

27. Langlois, J.-B., Emery, D., Mareda, J. & Alexakis, A. Mechanistic identification and improvement of a direct enantioconvergent transformation in copper-catalyzed asymmetric allylic alkylation. *Chem. Sci.* **3,** 1062–1069 (2012).

28. Ito, H., Kunii, S. & Sawamura, M. Direct enantio-convergent transformation of racemic substrates without racemization or symmetrization. *Nat. Chem.* **2,** 972–976 (2010).

29. You, H., Rideau, E., Sidera, M. & Fletcher, S. P. Non-stabilized nucleophiles in Cu-catalysed dynamic kinetic asymmetric allylic alkylation. *Nature* **517,** 351–355 (2015).

30. Sidera, M. & Fletcher, S. P. Cu-catalyzed asymmetric addition of sp2 - hybridized zirconium nucleophiles to racemic allyl bromides. *Chem. Commun.* **51,** 5044–5047 (2015).

31. Hamilton, J. Y., Sarlah, D. & Carreira, E. M. Iridium-catalyzed enantioselective allylic vinylation. *J. Am. Chem. Soc.* **135,** 994–997 (2013).

32. Yin, J. & Buchwald, S. L. A Catalytic Asymmetric Suzuki Coupling for the Synthesis of Axially Chiral Biaryl Compounds. *J. Am. Chem. Soc.* **122,** 12051–12052 (2000).

33. Baudoin, O. The asymmetric Suzuki coupling route to axially chiral biaryls. *Eur. J. Org. Chem.* 4223–4229 (2005).

34. Lovering, F., Bikker, J. & Humblet, C. Escape from flatland: Increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **52,** 6752–6756 (2009).

35. Clemons, P. a *et al.* Small molecules of different origins have distinct distributions of structural complexity that correlate with protein-binding profiles. *Proc. Natl. Acad. Sci. U. S. A.* **107,** 18787–18792 (2010).

36. Sakai, M., Hayashi, H. & Miyaura, N. Rhodium-Catalyzed Conjugate Addition of Aryl- or 1-Alkenylboronic Acids to Enones. *Organometallics* **16,** 4229–4231 (1997).

37. Hayashi, T., Takahashi, M., Takaya, Y. & Ogasawara, M. Catalytic Cycle of Rhodium-Catalyzed Asymmetric 1 , 4-Addition of Organoboronic Acids . Arylrhodium , Oxa- π -allylrhodium , and Hydroxorhodium Intermediates. *J. Am. Chem. Soc.* **124,** 5052–5058 (2002).

38. Trost, B. M. & Thaisrivongs, D. A. Strategy for employing unstabilized nucleophiles in palladium-catalyzed asymmetric allylic alkylations. *J. Am. Chem. Soc.* **130,** 14092–14093 (2008).

39. Puchot, C. *et al.* Nonlinear effects in asymmetric synthesis. Examples in asymmetric oxidations and aldolization reactions. *J. Am. Chem. Soc.* **108,** 2353–2357 (1986).