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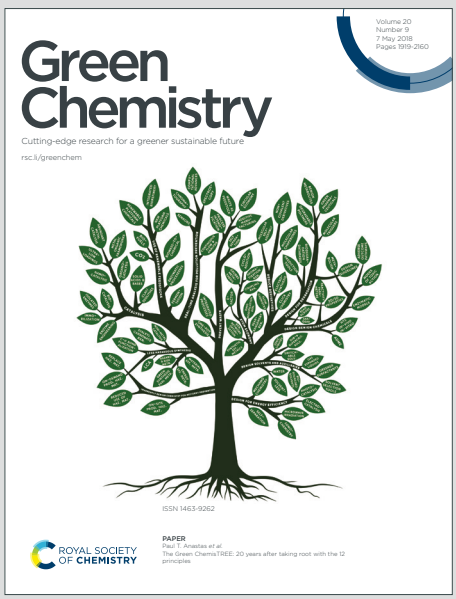

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Catalytic asymmetric synthesis of chiral phenols in ethanol with recyclable rhodium catalyst

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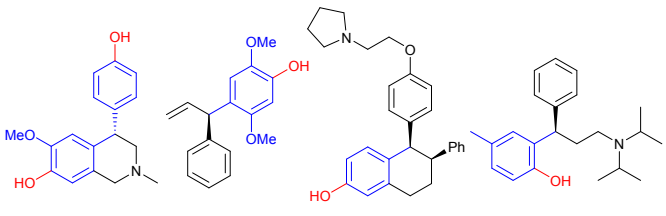
A general method to access diverse chiral phenols by rhodium-catalyzed asymmetric conjugate arylation using hydroxylated arylboronic acids in ethanol was developed. Recycling of the rhodium catalyst by flash chromatography on silica gel was feasible in this system. The synthetic utility of the strategy was demonstrated by efficient synthesis of chiral drug tolterodine.

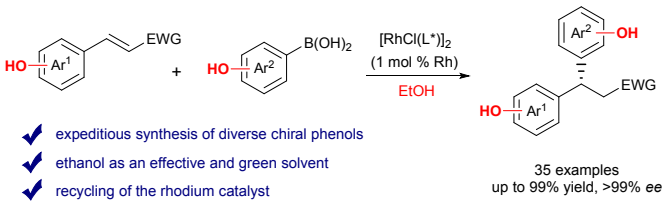
Phenols have been regarded as an important class of organic compounds because of their versatility in organic synthesis and remarkable significance in medicinal chemistry.[1] As a subset, chiral phenols bearing a benzylic stereogenic center represent an important class of structural motifs, which constitute the framework of many natural products and active pharmaceutical ingredients (APIs). Examples include cherylline isolated from *Crinum powellii*,[2a] mimosifoliol from the rootwood of *Aeschynomene mimosifolia*,[2b] lasofoxifene as a selective estrogen receptor modulator,[2c] and the blockbuster drug (*R*)-tolterodine[2d] (Fig. 1). Therefore, asymmetric synthesis of chiral phenols is of great synthetic interest, and considerable efforts have been devoted to this goal. Derivatization of chiral precursors provides a useful approach to chiral phenols, however, it inevitably leads to compromised step and atom economy. Taking advantage of the inherent reactivity of phenol in electrophilic aromatic substitution reactions, chiral phenols can be directly generated by asymmetric Friedel–Crafts or oxa-Pictet–Spengler reaction.[3] Asymmetric conjugate addition to *para*-quinone methides also led to the formation of chiral phenol derivatives.[4] 4-Hydroxylated phenylboronic acid was compatible with the Pd-catalyzed enantioselective 1,1-diarylation of acrylates, thus generating optically active phenols.[5] In spite of these significant advances, development of a general and green strategy that features high reactivity, excellent enantioselectivity, and broad substrate scope, which are essential for practical applications, is still highly desirable.



cherylline (+)-mimosifoliol lasofoxifene (*R*)-tolterodine

Fig. 1 Selected examples of natural products and APIs featuring the chiral phenolic motif.

The rhodium-catalyzed asymmetric conjugate arylation reaction using arylboronic acids represents one of the most reliable methods for synthesizing chiral molecules bearing a benzylic stereogenic center.[6,7] We envisioned that this catalytic system might be applied to the effective synthesis of chiral phenols, with the use of hydroxylated arylboronic acids. However, early studies showed that the presence of phenol would deactivate the rhodium catalyst,[8] and there have been rare examples using hydroxylated arylboronic acid/ester in rhodium-catalyzed arylation reactions.[9] Lautens and co-workers developed an elegant approach to (di)aza-dihydrodibenzoxepines by Rh/Pd domino catalysis,[9a,b] in which *ortho*-hydroxylated arylboronic ester was used for the conjugate addition step, with the need of stoichiometric amount of base. Herein we report a new reaction system for diverse hydroxylated arylboronic acids and phenolic substrates under rhodium catalysis, providing an expeditious route to various chiral phenols in a sustainable manner (Scheme 1). It is



- expeditious synthesis of diverse chiral phenols
- ethanol as an effective and green solvent
- recycling of the rhodium catalyst

35 examples
up to 99% yield, >99% *ee*

Scheme 1 Synthesis of chiral phenols by rhodium-catalyzed asymmetric addition.

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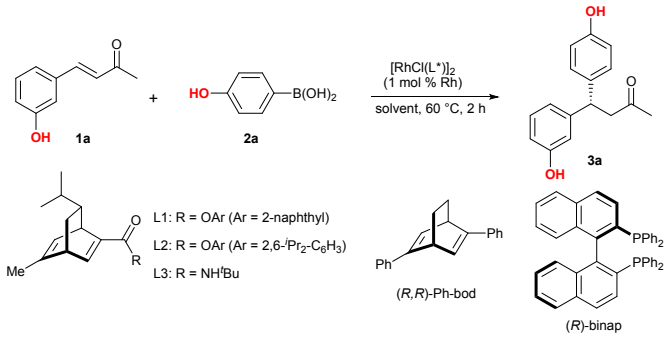
noteworthy that the reaction proceeds in ethanol, which is one of the recommended solvents for green synthesis.[10] Moreover, the reaction employs a stable chiral diene–rhodium(I) μ-chloro dimer as the catalyst under base-free conditions for most examples, and the catalyst can be recycled after easy separation by flash chromatography on silica gel.

As shown in Table 1, we commenced our investigation with a model reaction between two phenolic substrates, the phenolic enone **1a** and 4-hydroxyphenylboronic acid **2a**. Initially, we tested the reaction using a chiral diene L1-ligated rhodium catalyst (1 mol % Rh) in toluene/H_2O.[11] The reaction was not fully suppressed (entry 1), and a higher yield was obtained without base (entry 2). A significant solvent effect was observed, and it is interesting to observe a general trend that the solvent with better water miscibility gave a higher yield (entries 2–6), and ethanol was identified as the best solvent (entry 6, 99% yield, 97% *ee*). Further studies revealed that water was not essential (entries 7–8). The reaction also proceeded in pure water, but a diminished yield was obtained (entry 9). Other chiral ligands including dienes L2,[12] L3,[13] and (*R*,*R*)-Ph-bod,[14] as well as bisphosphine (*R*)-binap were also studied. All the catalyst gave **3a** in high yields, but the *ee* value was not further

Table 1 Rhodium-catalyzed asymmetric conjugate addition to phenolic enone **1a** with 4-hydroxyphenylboronic acid **2a**[a]



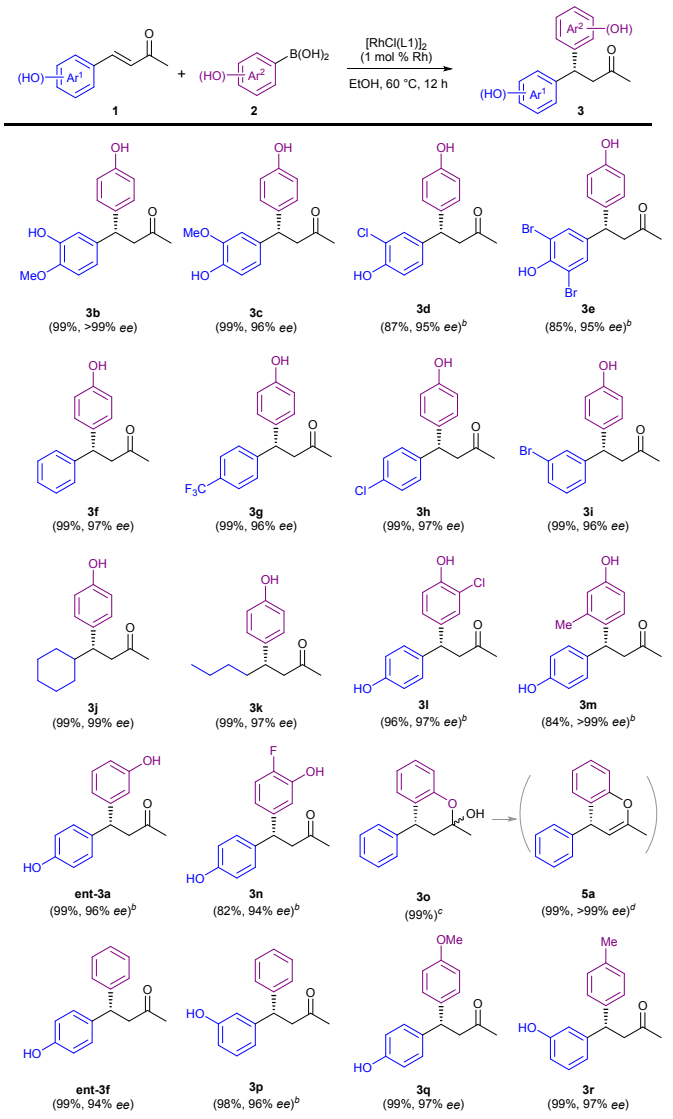
Entry	Ligand (L*)	Solvent/additive	Yield[b] (%)	*ee*[c] (%)
1	L1	toluene/H_2O[d]	25	95
2	L1	toluene/H_2O	31	95
3	L1	DCE/H_2O	29	97
4	L1	THF/H_2O	68	97
5	L1	dioxane/H_2O	74	97
6	L1	EtOH/H_2O	99	97
7	**L1**	**EtOH**	**99**	**97**
8	L1	EtOH[e]	99	97
9	L1	H_2O	48	94
10	L2	EtOH	99	92
11	L3	EtOH	99	97
12	(*R*,*R*)-Ph-bod	EtOH	99	53
13	(*R*)-binap	EtOH	83	8
14	L1	EtOH/PhOH[f]	99	97
15	L1	EtOH/PhOH[g]	99	97
16	L1	EtOH/AcOH[f,h]	90	96
17	L1	EtOH/$PhCO_2H$[f,h]	99	97

[a]Reactions were performed with **1a** (0.20 mmol), **2a** (0.30 mmol), and Rh catalyst (1 mol % Rh) in solvent (1.0 mL, 0.10 mL water was added if used) at 60 °C for 2 h. [b]Yield of the isolated **3a**. [c]Determined by HPLC analysis. [d]KOH (5 mol %) was added. [e]Anhydrous solvent was used. [f]Acid (5 mol %, 5 equiv. to Rh) was added. [g]100 equiv. to Rh was added. [h]0.40 mmol of **2a**, 12 h.

improved (entries 10–13). At last, acidic additives were investigated, and phenol (5 or 100 equiv. to Rh) was found to be fully compatible with the current reaction system (entries 14–15). Surprisingly, with stronger acids like acetic acid and benzoic acid as the additive (5 equiv. to Rh), the reaction still proceeded well (entries 16–17), which represents the first example showing the compatibility of rhodium-catalyzed arylation reaction with Brønsted acid additives.[15]

With the optimal conditions, the generality of the current system was investigated. As summarized in Table 2, phenolic enones bearing diverse substitutions were found to be compatible with the current system (**3b–3e**). Notably, site-selective mono-protected catechol derivatives can be readily obtained (**3b–3c**). Non-phenolic enones, including the aryl (**3f–3i**) and alkyl (**3j–3k**) ones, were well-tolerated. In addition to 4-hydroxyphenylboronic acid, hydroxylated phenylboronic acids bearing different substitutions at different positions were also

Table 2 Substrate scope[a]

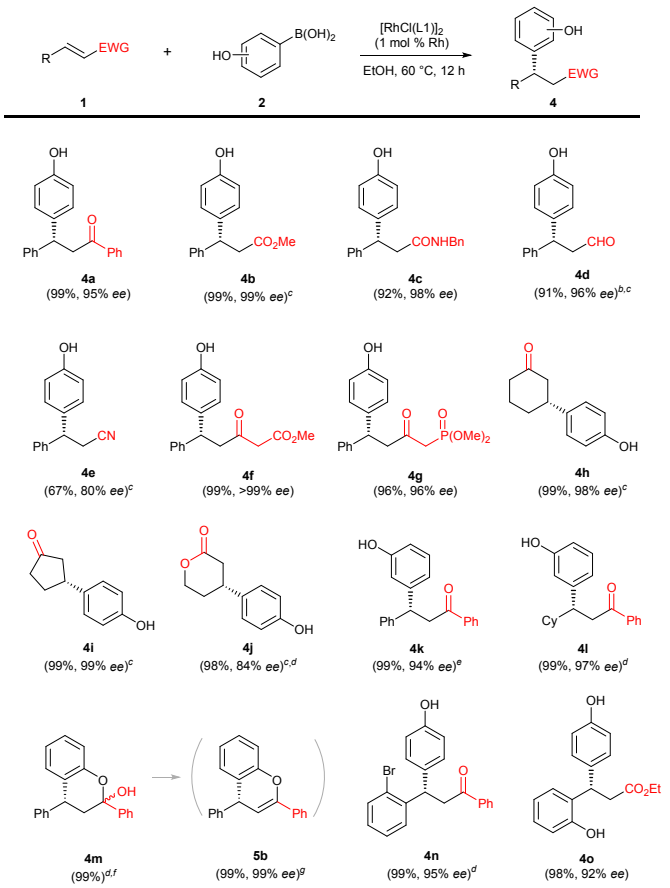


[a]**1** (0.20 mmol) and **2** (0.30 mmol). [b]at 80 °C. [c]0.40 mmol of **2** was used, and KOH (5 mol %) was added. [d]Dehydration condition: $TsOH·H_2O$ (10 mol %), 4 Å MS, toluene, 100 °C, 3 h.

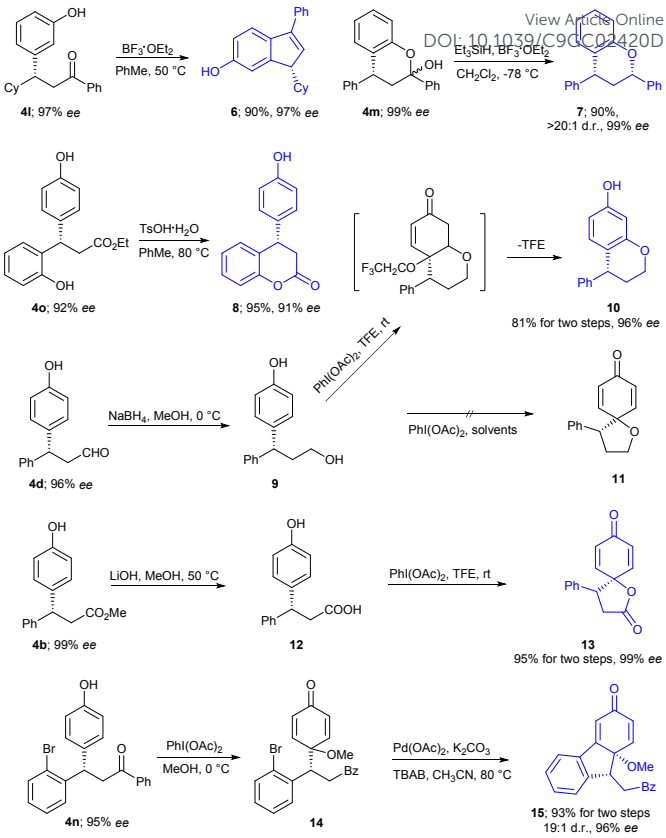
suitable (**3l–3n**). The addition product from 2-hydroxyphenylboronic acid readily cyclized to give a hemiacetal product (**3o**), which was dehydrated to produce the chiral chromene (**5a**). In addition, non-hydroxylated arylboronic acids (ent-**3f–3r**) worked equally well, showing the broad scope of the current system.

To further expand the scope of the current system, we next examined the substrates bearing different functional groups, and the results are summarized in Table 3. The substrates with benzoyl (**4a**), ester (**4b**), amide (**4c**), and aldehyde (**4c**) functional groups were all well-tolerated, and universal high yields and excellent enantioselectivities were obtained. The challenging α,β-unsaturated nitrile also worked, although a diminished yield and *ee* value was obtained (**4e**). The substrates with β-ketoester and β-ketophosphonate groups also worked well, producing valuable 1,3-dicarbonyl (**4f**) and Horner–Wadworth–Emmons reagent (**4g**) bearing chiral phenol motifs. Cyclic ketones and lactone were also suitable substrates (**4h–4j**). In addition, *meta*- and *ortho*-hydroxylated phenylboronic acids, as well as substrates with different substitutions were all well-tolerated (**4k–4o**). Note that catalytic amount of base was added to achieve a higher yield in several cases. The extraordinary functional group compatibility distinguishes the current method from other known.

Table 3 Scope of substrates with different functional groups[a]



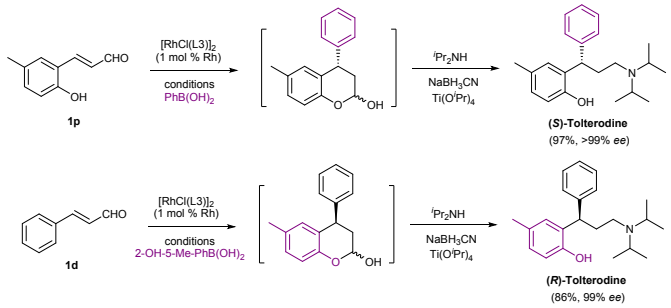
[a]**1** (0.20 mmol) and **2** (0.30 mmol). [b]at 50 °C. [c]L3-ligated rhodium catalyst was used. [d]KOH (5 mol %) was added. [e]at 80 °C. [f]0.40 mmol of **2** was used. [f]Dehydration condition: TsOH·H_2O (10 mol %), 4 Å MS, toluene, 100 °C, 3 h.



Scheme 2 Synthetic transformations of the chiral phenol products.

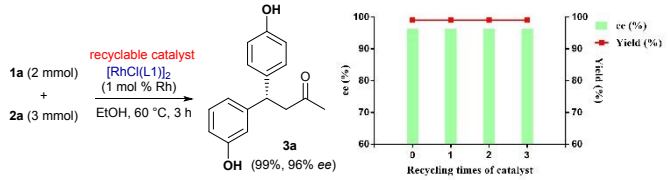
As depicted in Scheme 2, several stereospecific derivatizations of the chiral phenol products were conducted to demonstrate their synthetic utility. An intramolecular Friedel–Crafts type reaction of chiral phenol produced the chiral indene product (**4l** to **6**). The hemiacetal product can be directly reduced to the corresponding chromane with excellent diastereoselectivity (**4m** to **7**, >20:1 d.r.).[16] Chiral dihydrocoumarin **8** was easily obtained by intramolecular transesterification of **4o**. Oxidative transformations of different phenolic products with iodobenzene diacetate[17] were conducted to give diverse structures. For example, alcohol **9** underwent a formal dehydrogenation reaction under oxidative conditions to give the chiral chromane **10**. Spiro lactone **13** was obtained from phenolic carboxylic acid **12**. Oxidation of chiral phenol **4n** followed by an intramolecular Mizoroki–Heck reaction provided a convenient way to the fused-ring structure with excellent diastereocontrol (**15**).

The utility of the developed method was further demonstrated through a highly efficient two-step asymmetric synthesis of tolterodine,[18] a blockbuster drug used to treat overactive baldder to relieve urinary difficulties.[2d] As shown in Scheme 3, either combination (hydroxylated cinnamaldehyde with arylboronic acid or cinnamaldehyde with hydroxylated arylboronic acid) worked well to produce the key hemiacetal intermediate, which was directly converted to tolterodine by reductive amination in high yields with >99% enantioselectivities.



Scheme 3 Application in two-step asymmetric synthesis of tolterodine.

As shown in Scheme 4, the model reaction was scaled up to demonstrate the practicality of the current method (2 mmol scale, 0.51 g of **3a**, 99% yield, 96% *ee*). It is found that the chiral diene–rhodium(I) μ-chloro dimer remained in the system after completion of the reaction, and it can be easily recovered by flash chromatography on silica gel. It should be noted that the catalyst was recovered as a mixture with phenol (formed during the reaction by protodeboronation of **2a**), and the mixture was directly used for the recycling.[19] The catalyst was recycled for additional 3 times, and no erosion of the yield and enantioselectivity was observed. This recycling represents a rare case for rhodium catalysis in a homogeneous system.[20]



Scheme 4 Recycling of the catalyst.

In summary, we have developed a highly versatile method for the synthesis of chiral phenols under rhodium catalysis. The new method features low catalyst loading, high reactivity, and excellent enantioselectivity aside from displaying a broad substrate scope and functional group compatibility. The synthetic utility of the new method was demonstrated through useful synthetic transformations and synthesis of the chiral drug tolterodine. In addition, the reported method employs ethanol as the solvent with a recyclable catalyst, thus representing a green and sustainable synthetic approach to chiral phenols.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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