Palladium Catalyzed Enantioselective Hayashi-Miyaura Reaction for Pharmaceutically Important 4-Aryl-3,4-Dihydrocoumarins

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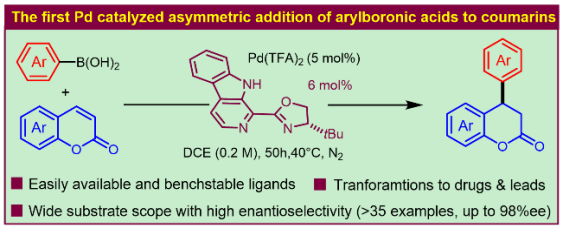
Supporting Information Placeholder

[

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The first palladium-catalyzed asymmetric addition of arylboronic acids to coumarins was successfully established, providing a straightforward asymmetric approach to achieving pharmaceutically important 4-aryl-3,4-dihydrocoumarins. This methodology features easily accessible and bench-stable ligands, a wide substrate scope, mild conditions and good accommodation of challenging, electron-withdrawing arylboronic acids.

Coumarins are pharmaceutically important characteristics in numerous bioactive natural products and synthesized drug leads, holding various activities ranging from anti-inflammatory, antioxidant, antimicrobial, to immunomodulatory properties.[1] Among different analogs, 4-aryl-3,4-dihydrocoumarins have attracted increasing attention from both synthetic communities and medicinal unions (Figure 1). Notably, dihydrocoumarins **1** and **2** showed outstanding anti-inflammatory and antioxidant activities.[1a] These coumarins can always serve as synthetic hubs for the construction of pharmaceutically important derivatives, exemplified by the GPR40 agonist 3,3-diarylpropanoic acid **3**[2] and the novel RORγ antagonists diphenylpropanamide ML209[3] and muscarinic antagonist (*R*)-tolterodine[4]. The pre-validated chiral differentiation of the biological effects[3] of 4-aryl-3,4-dihydrocoumarins and derivatives protruded the corresponding asymmetric synthesis as an important research topic.

Prominent advances in the asymmetric synthesis of 4-aryl-3,4-dihydrocoumarins (Figure 2A)[5] have been achieved through (1) hydroesterification of alkenylphenols **4**,[6] (2) asymmetric reduction of coumarins **5**,[7] (3) Baeyer-Villiger oxidation of indan-1-ones **6**,[8] (4) addition of 1,3-dicarbonyl compounds to *o*-quinone methides generated in situ from arylsulfonyl-alkylphenols **7**,[9] and (5) the addition of arylboronic acids to coumarins (Figure 2B). This privileged scaffold can also be prepared from enals **8** and phenols **9** through carbene-catalyzed annulation[10] or from *para*-quinone methides **10** *via* Rauhut-Currier reaction[11] (Figure 2A). Recently, Tang developed an elegant palladium/Wingphos-catalyzed asymmetric hydroesterification of diarylmethyl carbinols **11** to furnish chiral 4-aryl-3,4-dihydrocoumarins[12]. In the continuing interest in the asymmetric addition of arylboronic acids to *α,β*-unsaturated compounds[13] (Hayashi-Miyaura reactions), we envisage the asymmetric paradigm for the addition of arylboronic acids **12** to coumarins **13** is appealing given the versatility and facile availability of both reaction partners. Success in this will not only provide an alternative approach to the aforementioned bioactive products but also expand of the chemical space of complicated chiral dihydrocoumarins.

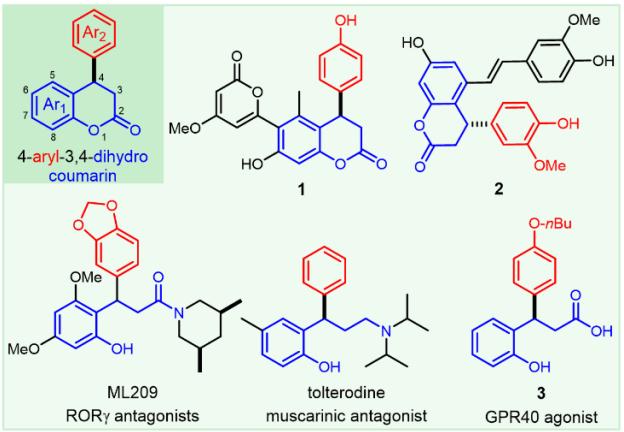


Figure 1. 4-Aryl-3,4-dihydrocoumarins relevant molecules

From a historical point of view, asymmetric addition of arylboronic acids to coumarins has mainly been realized by rhodium catalysis which was characterized by the development of various chiral biphosphorus ligands (Figure 2B-1). These advances were mainly showcased by the utilization of (*R*)-Segphos,[14] (MeO-F_{12}-BIPHEP),[15] modified BIPHEP **14**[16], (S)-BICMAP catalysts,[17] Chiraphos[18] and the air-sensitive phospholane phosphite ligand (*R, R, R*)-BOBPHOS from multistep synthesis.[19] Additionally, some

chiral diene ligands, such as ligand **15**[20] and ligand **16**[21] were also applied specifically.

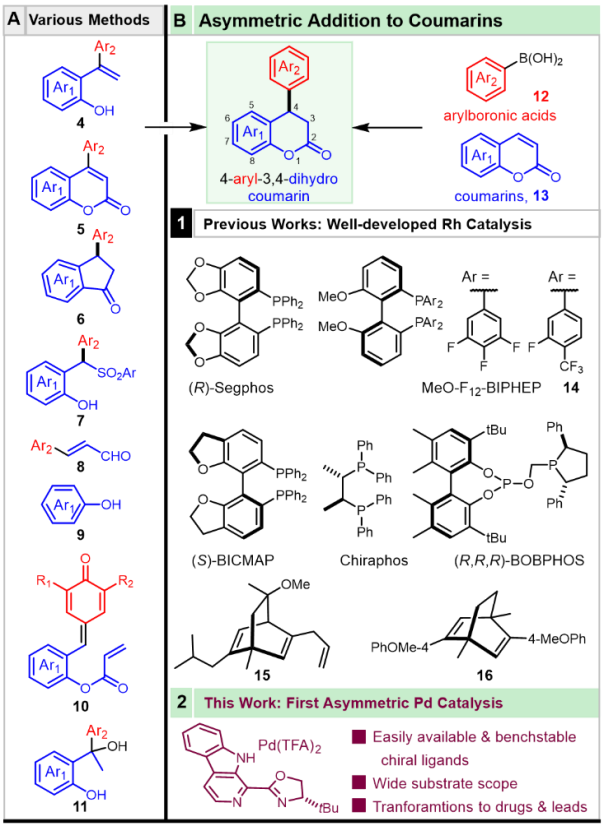
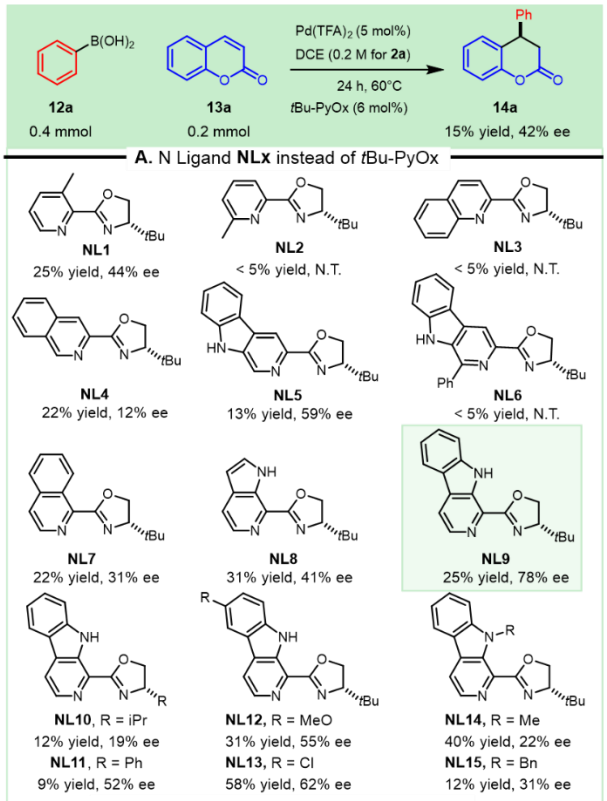


Figure 2. Various methods for 4-aryl-3,4-dihydrocoumarins

Notwithstanding some promising achievements, the aforementioned rhodium catalytic approaches encountered many challenges in view of synthetic feasibility and economy and the compatibility of electron-donating coumarins and electron-deficient or ring-fused arylboronic acids. Therefore, the discovery of novel catalytic systems with operational simplicity and facile accessibility is highly desirable for addressing these problematic issues. Our hypothesis was intrigued by the only example of the Pd/bipy system for the synthesis of diphenylpropanamides as RORγ antagonists[3]. It is noteworthy that this system was not tailored to the addition to coumarins but was applied immediately by just a horizontal transfer from that for *α,β*-unsaturated ketones and esters[22]. Palladium-catalyzed asymmetric addition is yet an untouched area and we envision the discovery of suitable catalysts is the key to overcoming this issue. Herein, we would like to document the first palladium catalytic system for the enantioselective addition of a large range of arylboronic acids to various coumarins (Figure 2B2). This protocol employs air-stable and easily accessible chiral ligands and can accommodate electron-poor arylboronic acids.

The identification of suitable chiral *N*-containing ligands commenced first for the Pd-catalyzed enantioselective addition of arylboronic acid **12a** to coumarin **13a** (Scheme 1A). Easily accessible PyOx-type ligands, including *t*Bu-PyOx, **NL1** and **NL2**, were initially investigated. The commonly used *t*Bu-PyOx can facilitate this transformation by delivering the desired compound **14a** in 42% enantiomeric excess (ee) with a modest isolated yield. The tiny increment of the steric hindrance near the coordinating position is not tolerant, as the 6-methyl-*t*Bu-PyOx **NL2** did not provide any detectable **14a**. Since ring-fused pyridine-oxazolines always provide new solutions for unprecedented transformations, we tested a large variation of (hetero)aryl fused pyridine-oxazoline ligands (**NL3**-**NL15**). Both quinoline-oxazoline **NL3** and *α*-phenyl *β*[3]-Carox **NL6** were inert to this addition, which may be due to the increased steric hindrance around the catalytic center. The isoquinoline-oxazolines **NL4** and **NL7**, slightly increased the production of **14a** at the cost of enantioselectivity. The introduction of an indole (**NL5**) or a pyrrole (**NL8**) backbone improved either the yield or the enantioselectivity of dihydrocoumarin **14a**. Gratifyingly, the orthogonal modification led to an attempt at using t-Bu-*β*[3]-Carox **NL9**, which allowed a significant improvement of the ee value to 78% ee.

Scheme 1. Optimization of the asymmetric addition of arylboronic acid **1a** to coumarin **2a**



B. Optimization of other parameters with **NL9**

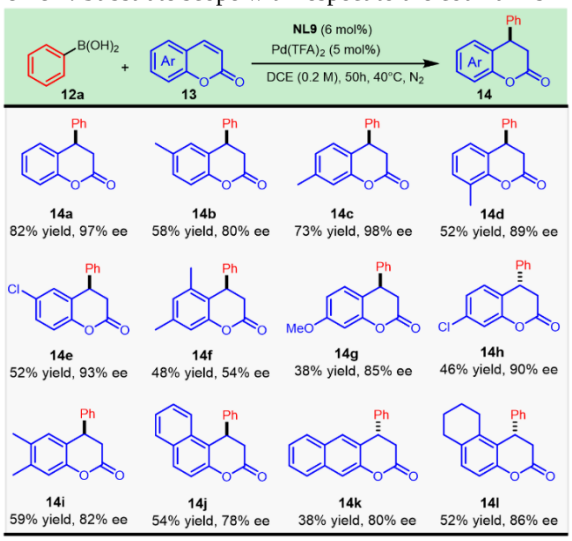
Entry	*Variation from Above Conditions*	Yield (%) [a]	ee (%) [b]
1	$CHCl_3$ instead of DCE	22	73
2	MeOH instead of DCE	<5 (35)[c]	N.T.
3	Dioxane instead of DCE	9	23
4	DMSO or MeCN instead of DCE	<5	N.T.
5	$Pd(OAc)_2$ instead of $Pd(TFA)_2$	<5 (42)[c]	N.T.
6	$Cu(OAc)_2$ or $Cu(TFA)_2$ instead of $Pd(TFA)_2$	<5	N.T.
7	2.5 mol% $Pd(TFA)_2$ with 3 mol% **NL9**	13	62
8	4 equiv. $PhB(OH)_2$	36	64
9	PhBPin or $(PhBO)_3$ instead of $PhB(OH)_2$	<5	N.T.
10	$PhBF_3K$ instead of $PhB(OH)_2$	27	83
11	under N_2 atmosphere	58	95
12	40°C instead of 60°C,N_2 atmosphere	58	98
13	0.4 M, N_2 atmosphere, 40°C	72	98
14	50 h, N_2 atmosphere, 40°C	82	97

Note [a], isolated yield; [b], detected by chiral HPLC on a chiralcel OD-H column (the absolute configuration was assigned by comparison with the literature); [c], the data in parentheses are the isolated yields of 4-Ph-coumarin

Tuning the steric factors on the oxazoline ring (**NL10** and **NL11**) or the electronic properties in the indole ring (**NL12**, **NL13**, **NL14**, and **NL15**) turned out to be inefficient. The other parameters (Scheme 1B) were subsequently optimized with the chiral ligand **NL9**. The variation of the reaction media revealed that the chlorinated polar solvent can provide a comparable result (entry 1), while DMSO or MeCN did not furnish detectable dihy-

drocoumarin **14a** (entry 4). The polar protic solvent methanol provided the Heck-type product 4-ph-coumarin in 35% yield (entry 2). A similar outcome was observed when the counterion was changed to CH_3COO^- (entry 5). Variation of the central metal to copper (entry 6) or a decrease in the catalyst loading (entry 7) was detrimental. Increasing the loading of $PhB(OH)_2$ can slightly improve the yield of **14a**, while a sharp erosion of the enantioselectivity was observed (entry 8). Dihydrocoumarin **14a** was also harvested by directly using $PhBF_3K$ (entry 10), while PhBPin or $(PhBO)_3$ was demonstrated to be inefficient (entry 9). Fruitful improvement was achieved by simply conducting the experiment under a N_2 atmosphere, in which the yield and enantioselectivity of **14a** were promoted to 58% and 95%, respectively (entry 11). The enantioselectivity was enhanced when the temperature was lowered to 40 °C without scarification of the conversion (entry 12). The conversion can be improved in a condensed solution (entry 13) or a prolonged process (entry 14). The optimal conditions, as shown in entry 14, provided 4-aryl-3,4-dihydrocoumarin **14a** in 82% yield and 97% ee.

Scheme 2. Substrate scope with respect to the coumarins [a]



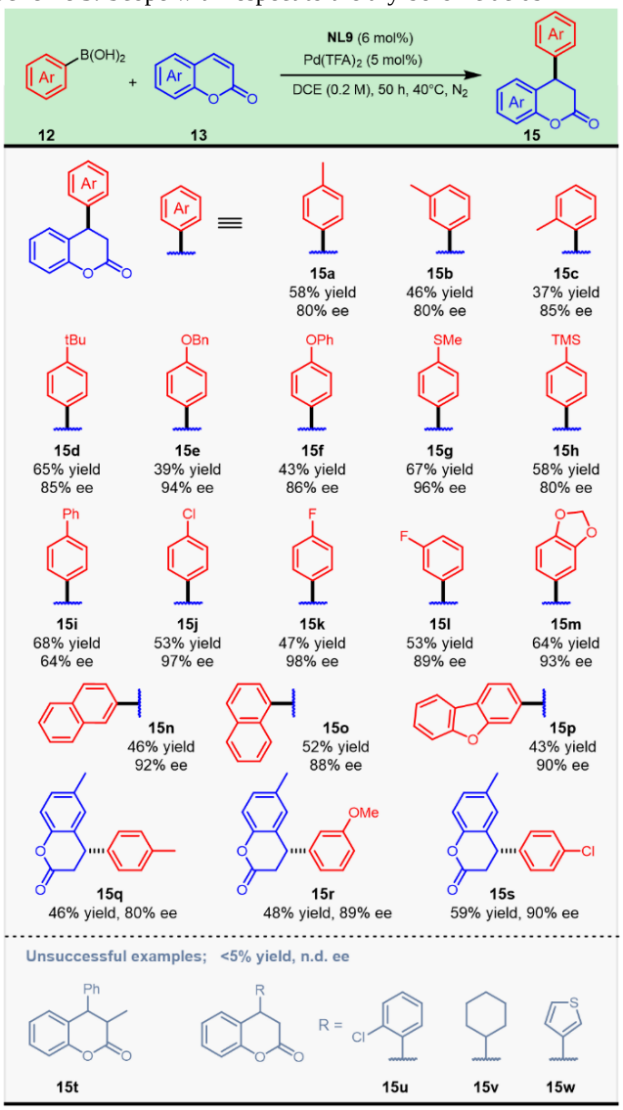
Note [a], All the yields refer to the isolated yield. The ee values were determined by HPLC on a chiral phase.

The optimized protocol has already proven to be capable of coupling the commercially available arylboronic acid **12a** with a variety of coumarins **13** (Scheme 2). Delightfully, different decorations with either electron-withdrawing or electron-donating groups on the aromatic segment could proceed smoothly to afford 4-phenyl-3,4-dihydrocoumarins with a good to an excellent stereocontrol. It is noteworthy that the dependence of the enantioselectivities on the substituted positions was observed. Migration of the methyl group from the 6-position to the 7-position or 8-position improved the enantioselectivity from 80% ee (**14b**) to 98% ee (**14c**) and 89% ee (**14d**), respectively. The problematic electron-donating coumarin in the rhodium catalysis[14] could also be converted with good enantioselectivity of 85% ee (**14g**). Shifting the chloro-group did not significantly affect the enantioselectivity and yields (**14e** and **14h**). Additional decoration of the methyl group to either the 5-position (**14f**) or 6-position (**14i**) demonstrated a deleterious effect on both productivity and selectivity compared with product **14c**. Interestingly, this method also promoted the ring-fused coumarins to react smoothly with phenylboronic acid **12a**. The fused position showed a negligible effect on the stereocontrol (**14j** vs. **14k**), while the [5,6]-fused isomer **14j** gave a more satisfying yield.

Our attention was turned to exploring the scope of the nucleophilic arylboronic acids **12** (Scheme 3). Delightfully, a wide variety of chiral 4-aryl-3,4-dihydrocoumarins could be achieved with good to excellent enantioselectivity. The generality was corroborated by the successful utilization of arylboronic acids with various functional groups, including ethers, thioether, halogens, fused rings and heterocycles. Although transferring the methyl group from the *para* or *meta* position to the *ortho* position impaired the reactivity (**15a** and **15b** vs. **15c**), slightly better enantioselectivity was detected due to the increased steric hindrance.

The similar variation of halogenated arylboronic acids showed a more sensitive effect on the enantioselectivity, exemplified by the preparation of compounds **15k** and **15l**. Notably, *para*-methylthio phenylboronic acid, which has a strong coordinating ability, did not impair either the reactivity or the enantioselectivity, providing **15g** in 67% isolated yield with up to 96% ee. The trimethylsilyl group was well tolerated, realizing the enantioselective synthesis of **15h** with a satisfactory yield. The challenging naphthylboronic acids in Rh catalysis,[17a] were successfully coupled with coumarin **13a** to deliver **15n** and **15o** in 92% ee and 88% ee, respectively. However, a limitation was observed when the 2,3-disubstituted coumarin (**15t**) or *ortho*-chloro-phenylboronic acid (**15u**) was recruited. The reaction was problematic by employing either aliphatic boronic acid (**15v**) or 3-thienyl boronic acid (**15w**).

Scheme 3. Scope with respect to the arylboronic acids [a]



Note [a], as in Scheme 2.

This method is anticipated to be of value for the asymmetric coupling of the electron-deficient arylboronic acids, which were challenging substrates in the previous Rh catalysis. Invigorated by the prevalidated examples (**15j**, **15k**, **15l** and **15s**) shown in Scheme 3, the compatibility of the current chemistry was further verified by enantioselective coupling fluoro-phenylboronic acids with various coumarins (Figure 3). Notably, 4-aryl-3,4-dihydrocoumarins **16e** and **16f** can be furnished in appreciable results in view of both yield and enantioselectivity, which contained unfavorable factors from both reaction partners.[14, 17a]

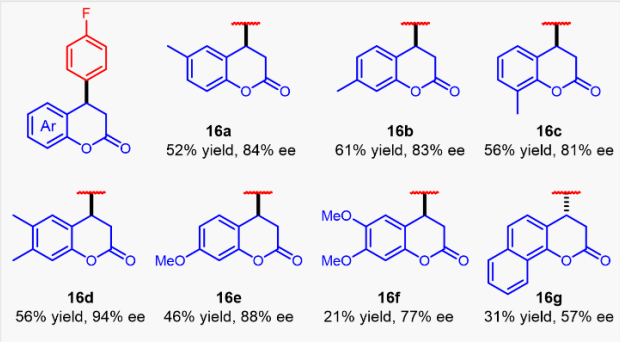


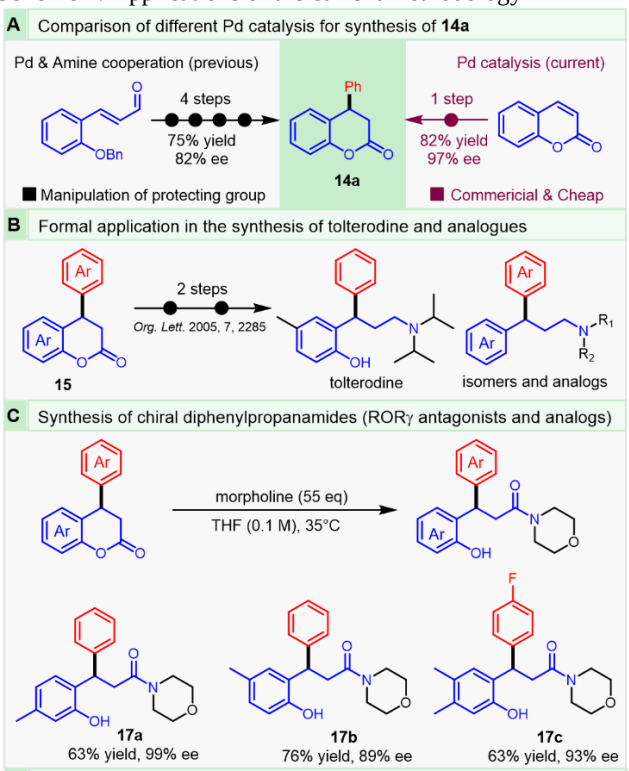
Figure 3. Asymmetric addition of *p*-fluoro-phenylboronic acid

Compared with the previous Pd/chiral amine co-catalysis for the enantioselective synthesis of 4-phenylchroman-2-one **14a**,[23] the current methodology represented a straightforward, convenient and higher enantioselective tactic (Scheme 4A). The current transformation will facilitate an alternative approach to the enantioselective synthesis of the urological drug (*R*)-tolterodine[14] or its isomers from 4-aryl-3,4-dihydrocoumarins **14b**, **14c** and **14d** (Scheme 4B). Additionally, compounds **15e**, **15f**, and **15g** (Scheme 3) could be transformed[12] to the enantioenriched *β*,*β*-diaryl carboxylic acids as analogs of potent GPR40 agonists for the treatment of diabetes. It is worth noting that aminolysis of the chiral 4-aryl-3,4-dihydrocoumarins with secondary amines will provide a modular and expeditious construction of a plethora of diphenylpropanamides, which have proven to be effective for treating T_H17-related autoimmune diseases.[24] The facile access to coumarins and the availability and variety of both arylboronic acids and amines may expand the chemical space of these pharmaceutically important amides.

Inspired by this late-stage amenability, we embarked on the aminolysis of 4-aryl-3,4-dihydrocoumarins to the corresponding amides, which can be deemed as the analogs of flumorph. The resulting enantioenriched amides **17a**-**17C** (Scheme 4C) can be readily acquired without decreasing the optical purity of the dihydrocoumarin precursors, highlighting the synthetic potential of this tactic. The in vitro antifungal phenotypic test (see the Supporting Information for more details) showed that the inhibitory efficacy of coumarin improved with the addition of arylboronic acid (Scheme 4D, **13b** vs. **14b**), while the corresponding product **17b** from aminolysis did not lead to further enhancement of antifungal potential. The resultant diphenylpropanamides demonstrated quite different antifungal potency from that of flumorph, showing that the unsaturated C=C bond of flumorph may be a crucial factor in acquiring significant antifungal potential against *phytophthora capsici*.

In summary, the first palladium-catalyzed asymmetric addition of arylboronic acids to coumarins was successfully established. This convenient protocol employed air-stable and easily accessible chiral nitrogen-containing ligands and provided a straightforward asymmetric approach to achieving pharmaceutically important 4-aryl-3,4-dihydrocoumarins. The generality was demonstrated by a successful asymmetric addition of various arylboronic acids to a wealth of coumarins. Notably, this methodology features mild conditions and accommodation of the challenging arylboronic acids encountered in the established Rh catalysts. Further progress is ongoing toward the discovery of novel pharmaceutically important leads through the synergistic interaction of synthetic methodologies and biological exploration.

Scheme 4. Applications of the current methodology



D Selected antifungal examples at 50 uM (inhibitory rate, %)

Compd.	*R.S.*	*S.S.*	*B.C.*	*F.G.*	*P.C.*	*P.O.*	*C.C.*
13b	0	0	17.3	0	7.4	28.6	16.3
***rac*-14b**	45.4	15.1	30.9	13.7	17.9	27.6	16.3
***rac*-17b**	0	3.8	29.4	1.2	34.7	27.6	12.8
***rac*-17c**	0	1.9	21.8	15.7	10.5	31.6	14.0
flumorph	2.8	5.7	23.6	0	97.9	10.2	12.8

R.S. : *Rhizoctonia solani*, ***S.S.*** : *Sclerotinia scleotiorum*, ***B.C.*** : *Botrytis cinerea*, ***F.G.***: *Fusarium graminearum*, ***P.C.*** : *Phytophthora capsici*, ***P.O.*** : *Pyricularia oryzae*, ***C.C.*** : *Colletotrichum capsici*.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Synthetic procedures, characteristic data, HPLC Traces, NMR spectra and antifungal data (file type, i.e., PDF)

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Author Contributions

S. Li conceived and designed this work, J. Lai and C. Yang performed experiments and provided the results, S. Li and J. Lai analyzed the data and all authors wrote the manuscript.

Notes

The authors declare no competing financial interest.

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