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Palladium-Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids to Heterocyclic Acceptors

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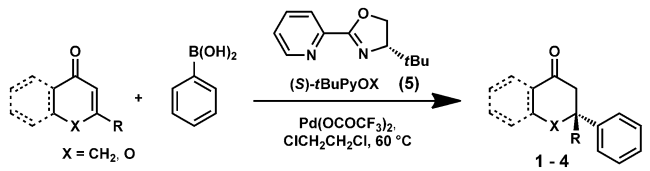
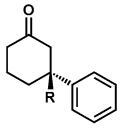
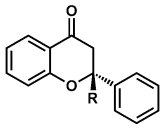
Palladium-catalyzed asymmetric conjugate additions are an increasingly versatile class of enantioselective reactions that allow stereoselective alkylation and arylation of α,β-unsaturated conjugate acceptors.[1] These processes often utilize easily-handled, air- and water-stable boron nucleophiles that render these reactions highly tolerant of oxygen and moisture.[2] Recently, our group disclosed the asymmetric conjugate addition of arylboronic acids to cyclic enones facilitated by a palladium catalyst derived in situ from palladium(II) trifluoroacetate and a chiral pyridinooxazoline (PyOX) ligand (**5**).[3] Notably, our catalyst system was generally applicable for five-, six-, and seven-membered carbocyclic enones. The numerous advantages of this system encouraged us to seek application to heterocyclic molecules to demonstrate the broad utility of this reaction for the synthesis of pharmaceutically relevant molecules. Herein, we report the first general enantioselective conjugate addition of arylboronic acids to heterocyclic conjugate acceptors derived from chromones and 4-quinolones utilizing the Pd/PyOX catalyst system. These reactions are performed under an atmosphere of air and deliver a large variety of asymmetric products with high enantioselectivity in moderate to excellent yields. The stereoselective conversion of chromones through conjugate addition renders access to flavanones, a class of heterocyclic molecules that has demonstrated numerous medicinal properties.[4] Recent literature suggests that intramolecular oxa-Michael additions are among the best-studied synthetic methods for asymmetric flavanone synthesis.[5] However, examples for the retrosynthetic disconnection of flavanones by conjugate addition of an aryl moiety to a chromone derivative remain scarce.[6,7] While chromones have been successfully employed in rhodium-catalyzed conjugate addition,[7] to the best of our knowledge, no palladium-catalyzed asymmetric conjugate addition syntheses of flavanones have been reported.[8] We identified chromone as a functioning conjugate acceptor with our Pd/PyOX system during a screen developed to analyze the effect of a β-substituent on reactivity and enantioselectivity (Table 1). As reported in our initial communication,[3] 3-methylcyclohexenone reacts with phenylboronic acid to give nearly quantitative yield of the conjugate addition adduct **2** in 93% *ee* (Table 1, entry 2). With only hydrogen in the β-position, enantioselectivity drops precipitously to 18% *ee* (Table 1, entry 1). Interestingly, 2-methyl-4-chromone reacts poorly, with only trace conjugate addition adduct detected by ^{1}H NMR spectroscopy (Table 1, entry 4), yet chromone reacts with high yield and excellent enantioselectivity (94% *ee*, Table 1, entry 3).

We sought to explore the scope of the asymmetric conjugate addition of arylboronic acids to chromones with respect to the range of substrates and functional groups tolerated. Moderate yields and enantioselectivity were realized with

Table 1. Comparison of asymmetric conjugate additions to various enone substrates.[a]



Entry	Product	Yield [%][b]	*ee* [%][c]
1	 **1** (R = H)	87[d]	18
2	**2** (R = Me)	99	93
3	 **3** (R = H)	91	94
4	**4** (R = Me)	trace	–

[a] Conditions: chromone (0.25 mmol), arylboronic acid (0.50 mmol), Pd(OCOCF$_3$)$_2$ (5 mol%), ligand (6 mol%), NH_4PF_6 (30 mol%), H_2O (5 equiv), $ClCH_2CH_2Cl$ (1 mL), 60 °C, 12 h. [b] Isolated yield. [c] *ee* determined by chiral SFC or HPLC. [d] No NH_4PF_6 was used.

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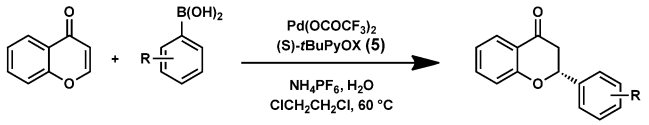
Table 2. Asymmetric conjugate addition of arylboronic acids to chromone.[a]



Entry	R	Yield [%][b]	*ee* [%][c]
1	H	91	94
2	2-F-C_6H_4	50	76
3	3-Me-C_6H_4	66	90
4	3-CO_2Me-C_6H_4	72	93
5	3-Br-C_6H_4	40	89
6	3-NH(CO)CF_3-C_6H_4	77	98
7	3-Cl-C_6H_4	52	94
8	4-Me-C_6H_4	64	94
9	4-Et-C_6H_4	36	85
10	4-F-C_6H_4	51	90
11	3,5-OMe-C_6H_3	69	95
12	4-dibenzofuran	64	77

[a] Conditions: chromone (0.25 mmol), arylboronic acid (0.50 mmol), Pd($OCOCF_3$)$_2$ (5 mol%), ligand (6 mol%), NH_4PF_6 (30 mol%), H_2O (5 equiv), $ClCH_2CH_2Cl$ (1 mL), 60°C, 12 h. [b] Isolated yield. [c] *ee* determined by chiral SFC.

sterically challenging 2-fluorophenylboronic acid (Table 2, entry 2). Arylboronic acid substitution at the *meta* position is generally tolerated with high enantioselectivity and moderate to good yields (Table 2, entries 3–7). Notably, arylboronic acids with halogen substitutents in the *para* position (Table 2, entry 10) and 3-carbomethoxyphenylboronic acid underwent conjugate addition with high enantioselectivity (Table 2, entry 4). Furthermore, nitrogen-containing substitution was well tolerated when protected as a trifluoroacetamide, producing the flavanone in 77% yield and 98% *ee* (Table 2, entry 6). Other *para*-substituted arylboronic acids also reacted with high enantioselectivity: alkyl substituents on the phenylboronic acid yielded 94% and 85% *ee* (Table 2, entries 8 and 9, respectively). With 3,5-dimethoxyphenylboronic acid, bearing multiple substituents, high enantioselectivity (95% *ee*) was obtained (Table 2, entry 11). Remarkably, a heteroarylboronic acid was successfully reacted with chromone as the conjugate acceptor for the first time (Table 2, entry 12), as 4-dibenzofuranboronic acid was converted with 64% yield and 77% *ee* in this case.

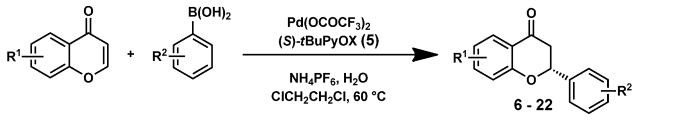
Substituted chromones were also found to perform well with the Pd/PyOX catalytic system. 5,7-Dimethyl-6-acetylchromone was successfully reacted with a variety of arylboronic acids (Table 3, i.e., **6**–**8**). Addition of phenylboronic acid gave nearly quantitative yield and 90% *ee* (**6**), while 3-methylphenylboronic acid displayed diminished yield with a comparable *ee* of 88% (**7**), and 4-ethylphenylboronic acid reacted with modest yield and 86% *ee* (**8**). Furthermore, a variety of *para*- and *meta*-substituted arylboronic acids were successfully converted with the corresponding 5,7-dimethyl-8-acetylchromone as well (i.e., **9**–**14**). Nucleophiles bearing functional group handles such as 3-carbomethoxyphenylboronic acid and 3-bromophenylboronic acid reacted to yield flavanone products **13** and **11**, respectively, with moderate yield (60% and 65%) and high *ee* (86% and 95%). Notably, with the present catalytic protocol 7-hydroxychromone could be successfully applied, yielding flavanones **18**, **19**, and **20** without protection of the phenol (Table 3). To our knowledge, this is the first example of an unprotected phenol reacted in asymmetric conjugate additions and serves to highlight the high functional group tolerance as compared to other systems.[7] 7-Hydroxychromone underwent smooth conjugate addition with a range of boronic acids in good yield and enantioselectivity: phenylboronic acid (**18**, 77% yield, 93% *ee*), 3-methylphenylboronic acid (**19**, 66% yield, 90% *ee*), and 4-fluorophenylboronic acid (**20**, 50% yield, 93% *ee*). Finally, we found reaction of phenylboronic acids with substituted chromones to be general for a number of other substituted chromones including 5,7-dimethylchromone (flavanones **15** and **16**, 92% *ee* and 95% *ee*), 7-acetoxychromone (flavanone **17**, 93% *ee*) and 7-methoxychromone (flavanones **21** and **22**, 94% *ee* and 96% *ee*).

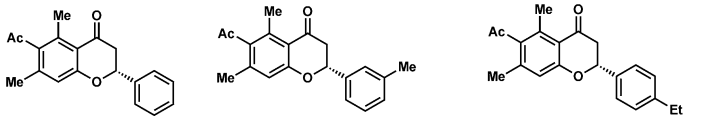
We next turned our attention to 4-quinolones as a class of potential substrates. Like flavanones, 4-quinolones have been reported as potential pharmaceutical agents.[9] Yet, despite their promising antimitotic and antitumor activity, the enantioselective synthesis of 2-aryl-2,3-dihydro-4-quinolones remains a challenge in asymmetric conjugate addition. Hayashi and co-workers reported a rhodium-catalyzed asymmetric conjugate addition, which utilized 3 equivalents of arylzinc chloride nucleophiles and superstoichiometic chlorotrimethylsilane to react with carboxybenzyl(Cbz)-protected 4-quinolones.[10] While Hayashi notes that phenylboronic acid is a particularly poor nucleophile in reactions with protected 4-quinolones, giving the desired conjugate addition adduct in only 10% yield, Liao and co-workers reported rhodium-catalyzed asymmetric 1,4-addition of sodium tetraarylborate reagents to *N*-substituted 4-quinolones.[11] To the best of our knowledge, there are no literature reports of palladium-catalyzed conjugate additions to 4-quinolones, nor are there any robust examples of additions to the latter utilizing simple boronic acid nucleophiles.

To our delight, Cbz-protected 4-quinolone reacted with phenylboronic acid to yield conjugate addition adduct **23** in modest yield and 80% *ee* (Table 4). Investigation of further *N*-protecting groups demonstrated that the Cbz-protected substrates gave the best results in terms of reactivity and stereoselectivity. Gratifyingly, a range of addition products could be prepared in up to 65% yield and 89% *ee* (Table 4). Nitrogen-containing, heteroaromatic and simpler boronic acid derivatives were successfully employed as nucleophiles in the 1,4-addition to 4-quinolones. For the corresponding alkyl- and halogen-substituted boronic acids, reasonable yields (45–65%) and enantioselectivities (67–89% *ee*) were observed.

Disubstituted boronic acids were well tolerated and gave similar results (**24** and **26**). Both compounds were obtained in 85% *ee*. For addition products **27**, **30**, and **31** yields and enantioselectivities ranging from 31% to 36% and 40% to

Table 3. Asymmetric conjugate addition of arylboronic acids to substituted chromones.[a]

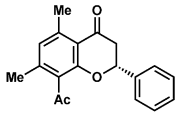




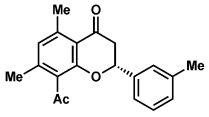
6
98 % yield
90 % *ee*

7
76 % yield
88 % *ee*

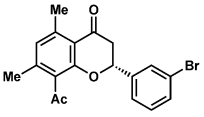
8
45 % yield
86 % *ee*



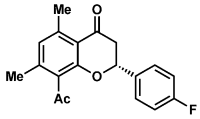
9
79 % yield
95 % *ee*



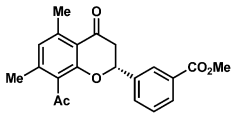
10
84 % yield
86 % *ee*



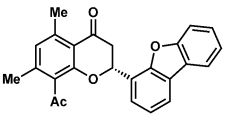
11
65 % yield
95 % *ee*



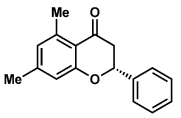
12
68 % yield
91 % *ee*



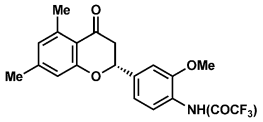
13
60 % yield
86 % *ee*



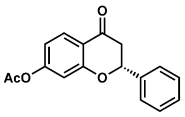
14
70 % yield
83 % *ee*



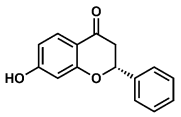
15
84 % yield
92 % *ee*



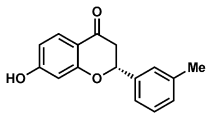
16
80 % yield
95 % *ee*



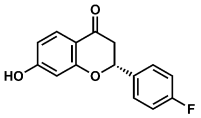
17
77 % yield
93 % *ee*



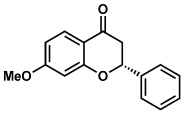
18
77 % yield
93 % *ee*



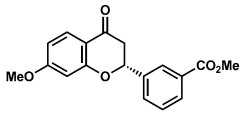
19
66 % yield
90 % *ee*



20
50 % yield
93 % *ee*



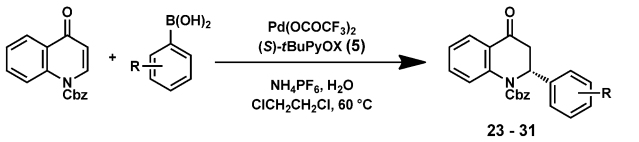
21
96 % yield
94 % *ee*

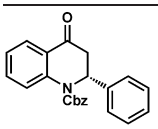


22
81 % yield
96 % *ee*

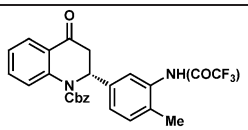
[a] Conditions: chromone (0.25 mmol), arylboronic acid (0.50 mmol), Pd-$(OCOCF_3)_2$ (5 mol %), Ligand (6 mol %), NH_4PF_6 (30 mol %), H_2O (5 equiv), $ClCH_2CH_2Cl$ (1 mL), 60 °C, 12 h, yields given are isolated yields, *ee* determined by chiral SFC.

Table 4. Asymmetric conjugate addition of arylboronic acids to 4-quinolones.[a]

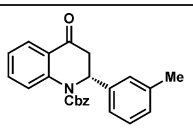




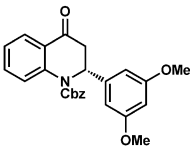
23
50 % yield
80 % *ee*



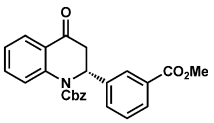
24
45 % yield
85 % *ee*



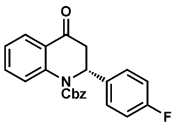
25
51 % yield
85 % *ee*



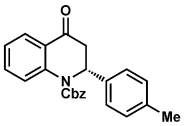
26
50 % yield
85 % *ee*



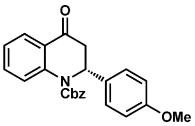
27
34 % yield
60 % *ee*



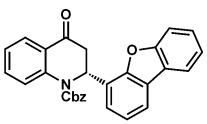
28
65 % yield
89 % *ee*



29
45 % yield
67 % *ee*



30
36 % yield
54 % *ee*



31
31 % yield
40 % *ee*

[a] Conditions: 4-quinolone (0.25 mmol), arylboronic acid (0.50 mmol), Pd-$(OCOCF_3)_2$ (5 mol %), ligand (6 mol %), NH_4PF_6 (30 mol %), H_2O (5 equiv), $ClCH_2CH_2Cl$ (1 mL), 60 °C, 12 h, yields given are isolated yields, *ee* determined by chiral SFC.

60 % *ee* were achieved (Table 4). While the decreased yield of quinolone **31** can be rationalized by the sterically demanding nature of the boronic acid, the lower *ee* could not be readily explained.

To confirm the homogeneous nature of our catalyst system and exclude the possibility of erosion of enantiomeric excess due to the presence of catalytically active, achiral palladium nanoparticles, a mercury drop test was performed. The addition of mercury to a catalytic reaction is widely used to exclude catalysis by palladium nanoparticles as the amalgamation should only deactivate heterogeneous metal particles.[12] For the conversion of chromone with phenylboronic acid in the presence of 200 equiv of mercury, with respect to the catalyst, only a slight drop of the yield from 91 % to 80 % was observed, while the *ee* of 94 % remained unaltered. Addition of mercury to the reaction of 3-methylcyclohexenone and phenylboronic acid resulted in quantitative yield and a slightly reduced *ee* of 90 % for addition product **2**, which is within error margins. Hence, the formation of zerovalent palladium nanoparticles could be excluded.

In conclusion, we report the palladium-catalyzed conjugate addition of arylboronic acids to chromones and 4-quinolones using a single, easily prepared catalyst system. To our knowledge this is the first report of a palladium-catalyzed asymmetric conjugate addition to chromones and 4-quinolones using either palladium catalysis or arylboronic acid nucleophiles. Overall, a total of 38 addition products could be synthesized in moderate to excellent yield and high enantioselectivity. The present catalytic protocol exhibits particularly mild reaction conditions and renders the use of

silver salts for catalyst activation obsolete. Furthermore, moisture and air are well tolerated; this results in an unprecedented functional group tolerance. Hence, the direct synthesis of flavanones bearing free hydroxyl groups by conjugate addition and the application of *N*-substituted, as well as heterocyclic boronic acids, is realized. We are currently conducting kinetic and computational studies to elucidate the present catalytic reaction mechanism. Furthermore, continued study of the substrate scope of the Pd/PyOX system and its reactivity, as well as the application of these operationally simple asymmetric conjugate addition reactions to total synthesis are underway in our laboratory.

Experimental Section

Representative general procedure for the enantioselective 1,4-addition of arylboronic acids to heteroaromatic conjugate acceptors: A screw-top 1 dram vial was charged with a stir bar, $Pd(OCOCF_3)_2$ (4.2 mg, 0.0125 mmol, 5 mol%), (*S*)-*t*BuPyOX (3.1 mg, 0.015 mmol, 6 mol%), NH_4PF_6 (12.5 mg, 0.075 mmol, 30 mol%), and the corresponding arylboronic acid (0.50 mmol, 2.0 equiv). The solids were suspended in dichloroethane (0.5 mL) and stirred for 2 min at ambient temperature, after which time a yellow color was observed. Not all solids were dissolved at this time. Conjugate acceptor substrate (0.25 mmol, 1.0 equiv) and water (0.025 mL, 1.25 mmol, 5.0 equiv) were added. The walls of the vial were rinsed with an additional portion of dichloroethane (0.5 mL). The vial was capped and the mixture was stirred at 60 °C in an oil bath for 12 h. Upon complete consumption of the starting material (monitored by TLC, 4:1 hexanes/EtOAc, *p*-anisaldehyde or iodine/silica gel stain) the reaction mixture was eluted through a pipet plug of silica gel, using CH_2Cl_2 as the eluent, and concentrated in vacuo. The crude residue was purified by column chromatography (hexanes/EtOAc) to afford a colorless solid.

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