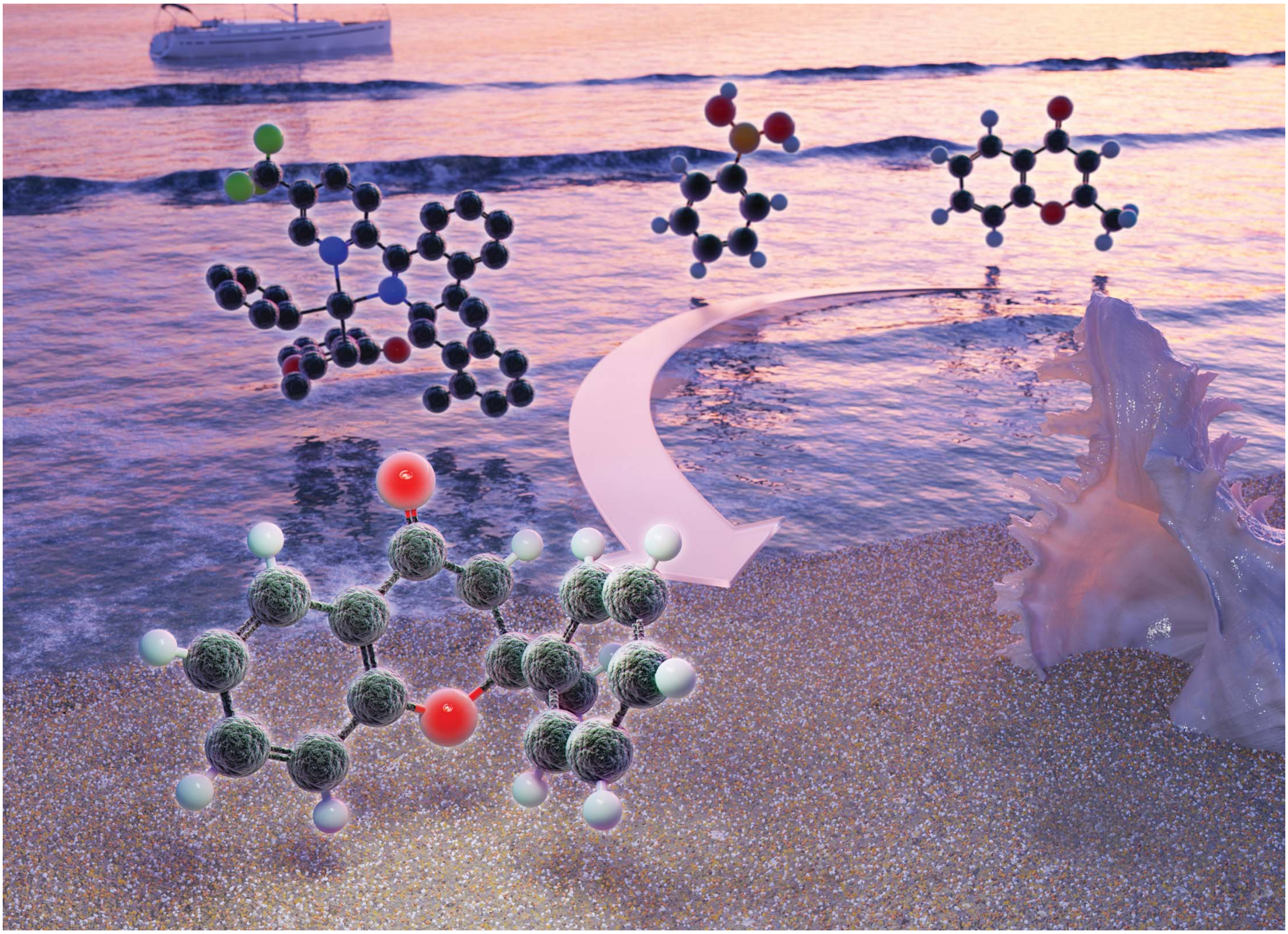

Showcasing research from Professor Stoltz's laboratory, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, USA, and Professor Hong's laboratory, Department of Chemistry, Gwangju Institute of Science and Technology, Gwangju, Republic of Korea.

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Catalytic enantioselective synthesis of tetrasubstituted chromanones *via* palladium-catalyzed asymmetric conjugate arylation using chiral pyridine-dihydroisoquinoline ligands†

Doohyun Baek,[a] Huijeong Ryu,[a] Ji Yeon Ryu,[b] Junseong Lee,[b] Brian M. Stoltz*[c] and Sukwon Hong*[ad]

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Highly enantioselective conjugate addition reactions of arylboronic acids to 2-substituted chromones catalyzed by palladium complexes with new chiral Pyridine-Dihydroisoquinoline (PyDHIQ) ligands have been developed. These reactions provide highly enantioselective access to chromanones containing tetrasubstituted stereocenters. Various arylboronic acids and 2-substituted chromones can be used in the catalytic reaction to afford the chiral tetrasubstituted chromanones in good yields and excellent enantioselectivities (25 examples, up to 98% yields, up to 99% ee).

Introduction

Optically active chromanone scaffolds having a stereocenter at the C2 position are prominent structural motifs in natural products, and possess numerous bioactivities (Scheme 1a).[1] Chiral chromanones have been synthesized by various methods,[2] such as intramolecular oxa-Michael additions,[3] asymmetric conjugate additions,[4] asymmetric reductions,[5] and Mitsunobu cyclizations.[6] Nevertheless, much of the previous research has focused on generation of trisubstituted rather than tetrasubstituted stereocenters. Direct asymmetric transformation to generate a tetrasubstituted oxygen-bearing stereocenter at the C2 position of chromanone has remained rather elusive. A sole exception was reported by the Kurth group, wherein the enantioselective synthesis of chiral tetrasubstituted spirocyclic chromanones was enabled *via* enamine-mediated aldol/oxa-Michael tandem reactions.[7] To the best of our knowledge, there have been no other examples demonstrating the enantioselective construction of tetrasubstituted stereocenters at the C2 position of chromanones in a single step.

Asymmetric conjugate addition reactions[8] can provide a straightforward pathway to chiral C2-tetrasubstituted chromanones from relatively simple, achiral unsaturated acceptors (*i.e.*, 2-substituted chromones). In 2013, the Stoltz group disclosed that 2-methylchromone is not a suitable electrophile for their well-established Pd(II)/PyOx[4e,9] catalyzed asymmetric conjugate addition chemistry[4e] (Scheme 1b).

Interestingly, the Stanley group later reported the racemic version of such a conjugate addition of arylboronic acids to 2-substituted chromones catalyzed by a Pd(II)/phenanthroline complex in aqueous media[10] (Scheme 1b). We envisioned that palladium-catalyzed asymmetric conjugate addition to 2-substituted chromones could be achieved by developing new chiral *N*,*N*-ligands, which can be effective in Stanley's aqueous conditions. We imagined that dihydroisoquinoline-based ligands, having chiral imine moieties, could be potential candidates. Herein, we report the first example of a palladium-catalyzed asymmetric conjugate addition of arylboronic acids to 2-substituted chromones with newly developed chiral *N*,*N*-ligands (Scheme 1c). This reaction provides highly enantioselective synthetic access to chiral chromanones bearing tetrasubstituted stereocenters in a single step.

Results and discussion

We have previously reported chiral dihydroisoquinoline-based N-heterocyclic carbene (NHC) ligands and (*N*,*N*) type diimine ligands, which were synthesized *via* Bischler–Napieralski cyclization.[11] Following a similar synthetic protocol, a series of chiral Pyridine-Dihydroisoquinoline (PyDHIQ) ligands were successfully prepared (Scheme 2). Electronic and steric properties of PyDHIQ ligands can be easily modulated by varying

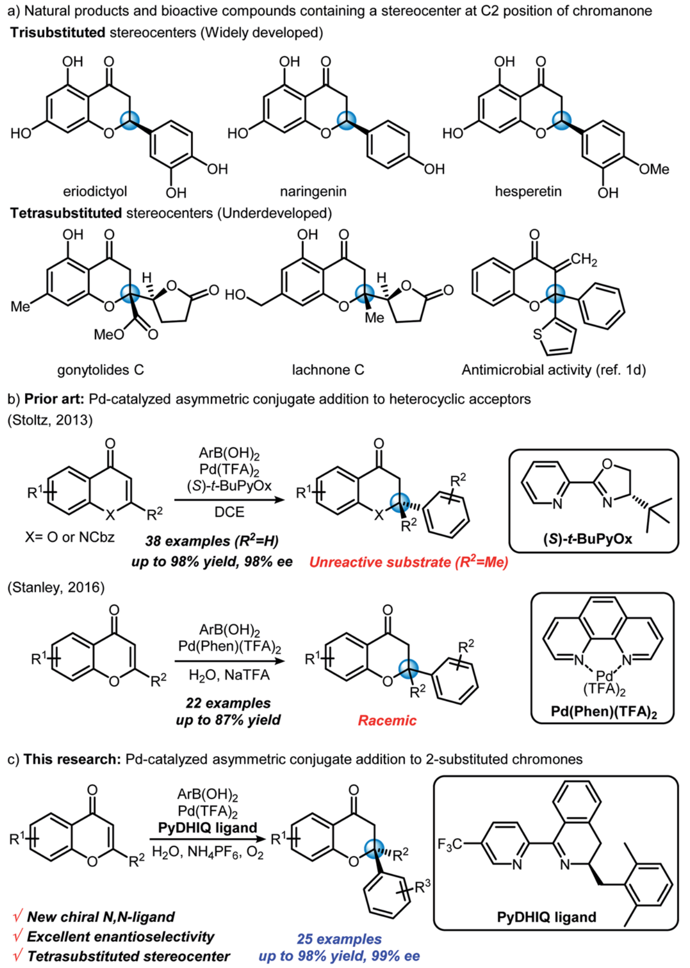
[a]Department of Chemistry, Gwangju Institute of Science and Technology, 123 Cheomdan-gwagiro, Buk-gu, Gwangju 61005, Republic of Korea. E-mail: shong@gist.ac.kr

[b]Department of Chemistry, Chonnam National University, 77 Yongbong-ro, Buk-gu, Gwangju 61186, Republic of Korea

[c]The Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA. E-mail: stoltz@caltech.edu

[d]School of Materials Science and Engineering, Gwangju Institute of Science and Technology, 123 Cheomdan-gwagiro, Buk-gu, Gwangju 61005, Republic of Korea

† Electronic supplementary information (ESI) available. CCDC 1843946 and 1954885. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc00412j



Scheme 1 Synthesis of chromanones by palladium-catalyzed conjugate addition to chromones.

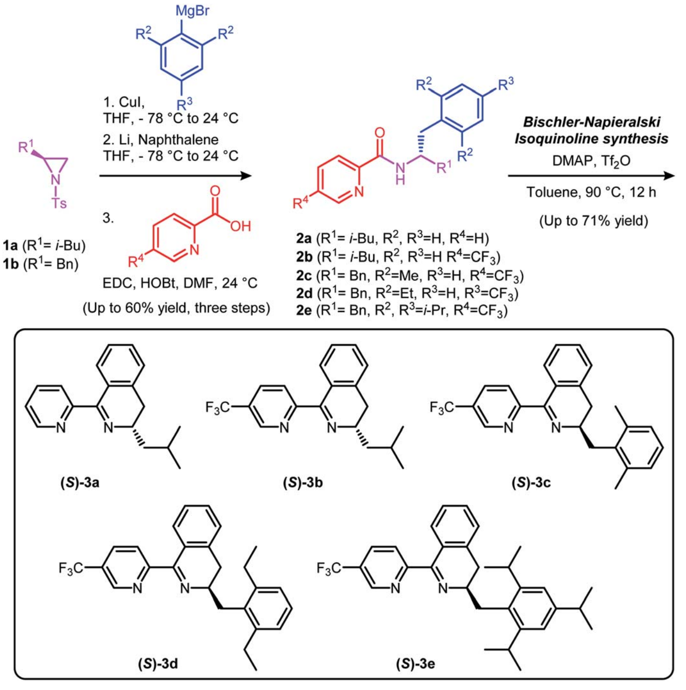
substituents of the pyridine as well as the stereodifferentiating groups of the chiral imine moiety ((**S**)-**3a**–**3e**).

With the chiral PyDHIQ ligands in hand, the asymmetric conjugate addition reaction of phenylboronic acid to 2-methylchromone was investigated by employing the PyDHIQ ligands, $Pd(TFA)_2$, H_2O as a solvent, and NH_4PF_6 as an additive[4e,10] (Table 1).

It is important to note that (**S**)-**t-BuPyOx** ligand showed no reactivity in the current reaction conditions (Table 1, entry 1). While (**S**)-**3a** also showed no reactivity, electronically modified ligand (**S**)-**3b** showed low reactivity and moderate enantioselectivity (Table 1, entries 2 and 3). Surprisingly, a considerable increase of both yield and enantioselectivity was observed with ligand (**S**)-**3c** which has a (2,6-dimethylphenyl)methyl group (Table 1, entry 4). When the steric demands were increased in the ligands (**S**)-**3d** and (**S**)-**3e**, enantioselectivity was increased at the expense of the yield (Table 1, entries 5 and 6). Therefore, the ligand (**S**)-**3c** was chosen for further study as it showed a balanced performance in terms of reactivity and enantioselectivity. Encouraged by these results, we systematically altered the reaction conditions and searched for potential additives to further improve reactivity and enantioselectivity. Weakly coordinating counteranions such as BF_4^- and PF_6^- were tested, since these have previously been shown to beneficially impact the reactivity and selectivity in related conjugate addition reactions.[9b] All the additives tested resulted in better reactivity than without the additive (*cf.* entries 8–10 with entry 7). PF_6^- showed higher yields than BF_4^- (entries 8 *vs.* 9, and entries 4 *vs.* 10) and ammonium cation showed higher yields than the sodium cation (entries 4 *vs.* 9 and entries 8 *vs.* 10). As a result, NH_4PF_6 was selected because it showed excellent reactivity and high enantioselectivity (entry 4). In addition, the use of *m*-chlorophenylboronic acids resulted in very low yields (entry 11). By increasing the reaction temperature from 60 °C to 70 °C, the yield increased from 17% to 33% (entry 12). The ligand decomposition was observed at 80 °C by thin-layer chromatography monitoring (entry 13).

Remarkably, O_2 atmosphere increased the isolated yield from 33% to 55% at 70 °C (entry 14).[12] Therefore, the optimized reaction conditions including the use of NH_4PF_6 in O_2 atmosphere at 70 °C showed the best combination of reactivity and enantioselectivity.

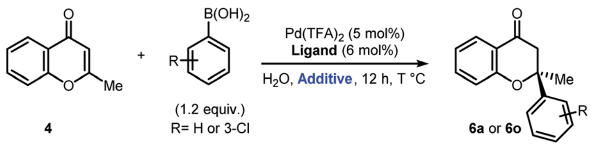
Under the optimized reaction conditions, the substrate scope was examined with various arylboronic acids (Table 2). In case of the reaction with *para*-substituted arylboronic acids, electron-rich boronic acids (Table 2, **6b**–**6e**) resulted in mostly good yields (78–85%) and high enantioselectivity (96–99%),



Scheme 2 Chiral pyridine-dihydroisoquinoline(PyDHIQ) ligands.

except for *para*-methoxyphenylboronic acid **6d** (51% yields and 90% ee). Reactions with electron-deficient boronic acids such as *para*-fluoro- or *para*-chlorophenylboronic acid also showed good reactivity and high enantioselectivity (Table 2, **6j** and **6k**). However, reduced yields were observed with *para*-bromophenylboronic acid (**6l**, 32% yield and 98% ee) and *para*-trifluoromethylphenylboronic acid (**6m**, 31% yield and 99% ee). In case of the reaction with *meta*-substituted arylboronic acids, electron-rich boronic acids (Table 2, **6f–6i**) showed good yield (77–82%) and high enantioselectivity (97–99%). An exceptional

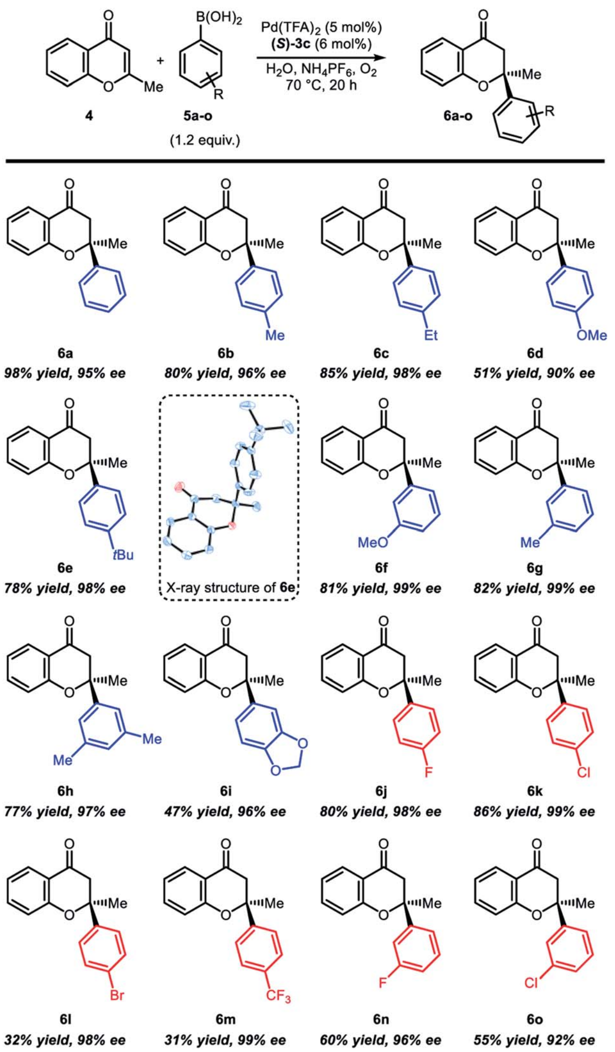
Table 1 Reaction optimization[a]



Entry	T [°C]	ArB(OH)$_2$	Additive (30 mol%)	Ligand	Yield[c] [%]	ee[d] [%]
1	60	PhB(OH)$_2$	NH_4PF_6	**(*S*)-*t*-BuPyOx**[b]	Trace	—
2	60	PhB(OH)$_2$	NH_4PF_6	**(*S*)-3a**	Trace	—
3	60	PhB(OH)$_2$	NH_4PF_6	**(*S*)-3b**	11	−68
4	60	PhB(OH)$_2$	NH_4PF_6	**(*S*)-3c**	**97**	**95**
5	60	PhB(OH)$_2$	NH_4PF_6	**(*S*)-3d**	77	98
6	60	PhB(OH)$_2$	NH_4PF_6	**(*S*)-3e**	70	98
7	60	PhB(OH)$_2$	—	**(*S*)-3c**	42	90
8	60	PhB(OH)$_2$	$NaBF_4$	**(*S*)-3c**	47	95
9	60	PhB(OH)$_2$	$NaPF_6$	**(*S*)-3c**	85	95
10	60	PhB(OH)$_2$	NH_4BF_4	**(*S*)-3c**	60	90
11	60	3-ClPhB(OH)$_2$	NH_4PF_6	**(*S*)-3c**	17	90
12	70	3-ClPhB(OH)$_2$	NH_4PF_6	**(*S*)-3c**	33	90
13	80	3-ClPhB(OH)$_2$	NH_4PF_6	**(*S*)-3c**	35	89
14	70	3-ClPhB(OH)$_2$	NH_4PF_6, O_2 balloon	**(*S*)-3c**	**55**	**92**

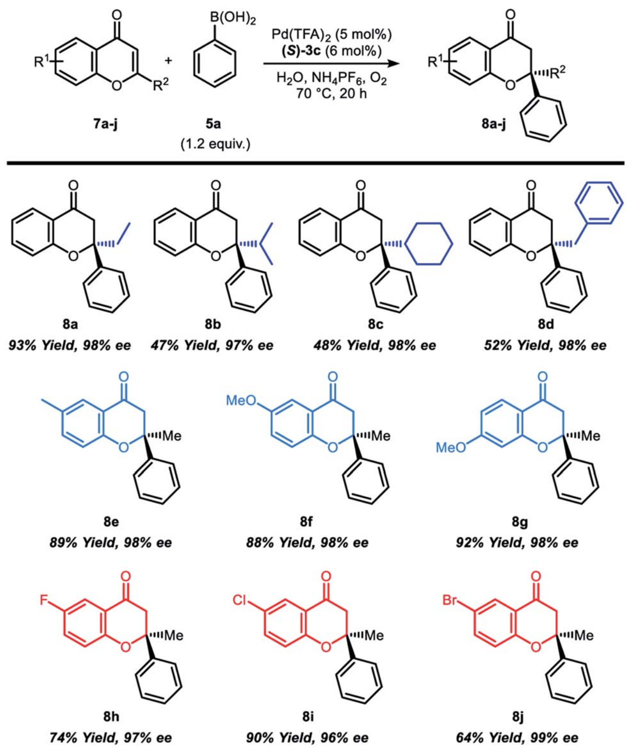
[a] All reactions were carried out with **4** (0.5 mmol, 1 equiv.), ArB(OH)$_2$ (0.6 mmol, 1.2 equiv.), Pd(TFA)$_2$ (0.025 mmol, 5 mol%), ligand (0.030 mmol, 6 mol%), additive (0.15 mmol, 30 mol%), H_2O (0.35 mL) for 12 h. [b] (*S*)-5-CF_3-*t*-BuPyOx also showed trace amount of products; see ESI for additional screening data. [c] Isolated yield of **6a** or **6o**. [d] Determined by HPLC with DAICEL chiralpak.

Table 2 Reaction scope of arylboronic acid nucleophiles[a,b]



[a] All reactions were carried out in vial charged with **4** (0.5 mmol, 1 equiv.), $ArB(OH)_2$ (0.6 mmol, 1.2 equiv.), $Pd(TFA)_2$ (0.025 mmol, 5 mol%), **(*S*)-3c** (0.030 mmol, 6 mol%), NH_4PF_6 (0.15 mmol, 30 mol%), H_2O (0.70 mL), and O_2 balloon for 20 h. [b] Isolated yield.

Table 3 Reaction scope of chromone electrophiles[a,b]



[a] All reactions were carried out in vial charged with **7** (0.5 mmol, 1 equiv.), $PhB(OH)_2$ (0.6 mmol, 1.2 equiv.), $Pd(TFA)_2$ (0.025 mmol, 5 mol%), **(*S*)-3c** (0.030 mmol, 6 mol%), NH_4PF_6 (0.15 mmol, 30 mol%), H_2O (0.70 mL), and O_2 balloon for 20 h. [b] Isolated yield.

case is 3,4-(methylenedioxy)phenylboronic acid **6i**, which was isolated in 47% yield and 96% ee. Reactions with electron-deficient arylboronic acids (**6n** and **6o**) were also isolated in moderate yields (55–60%) and high enantioselectivity (92–96%). The absolute configuration of compound **6e** was determined by X-ray crystallography, and all other products were assigned by analogy.

In sequence, the reaction scope was studied with various 2-substituted chromone derivatives (Table 3). 2-Ethyl-, 2-isopropyl-, 2-benzyl- and 2-cyclohexylchromones were synthesized according to previously reported literature[5b] to investigate the steric effect of 2-substituted chromones (Table 3, **8a–8d**). Reactions with 2-ethylchromone, which has a linear β-alkyl substituent resulted in excellent yield and high enantioselectivity (**8a**, 93% yield and 98% ee). On the other hand, chromones having a branched β-alkyl substituent such as isopropyl or cyclohexyl group afforded the product **8b** and **8c** in moderate yield (47–48%), but still with high enantioselectivity (97–98%). 2-Benzylchromone also displayed moderate reactivity with outstanding enantioselectivity (**8d**, 52% yield and 98% ee). Notably, both electron-rich and electron-deficient chromones with substituents at the 6-position or 7-position were well tolerated in the reaction (**8e–8j**), furnishing good yields (64–92%)and high enantioselectivity (96–99%).

The [**(*S*)-3d**]–Pd(II) complex was prepared by the complexation of **(*S*)-3d** with palladium(II) chloride and characterized by X-ray crystallography (Fig. 1a). The X-ray structure of [**(*S*)-3d**]$PdCl_2$ showed that Pd–Cl bond *trans* to the dihydroisoquinoline is slightly longer than Pd–Cl bond *cis* to the dihydroisoquinoline (2.287(2) Å *vs.* 2.280(2) Å).[13] This suggests that the dihydroisoquinoline would exert a stronger *trans* influence than the pyridine. Based on the literature precedence, it might be reasonable to propose a stereochemistry-determining transition state where a Pd–phenyl bond is located *trans* to the dihydroisoquinoline moiety (Fig. 1b).[9b,9g,12b,13] Fig. 1b shows our simplified transition state model rationalizing the stereochemical pathways of asymmetric conjugate addition of phenylboronic acid **5a** to 2-methylchromone **4**. It has been known that the enantioselectivity-determining step involves a square-planar geometry transition state at the stage when the phenyl group inserts across the alkene.[9b] Among the two possible

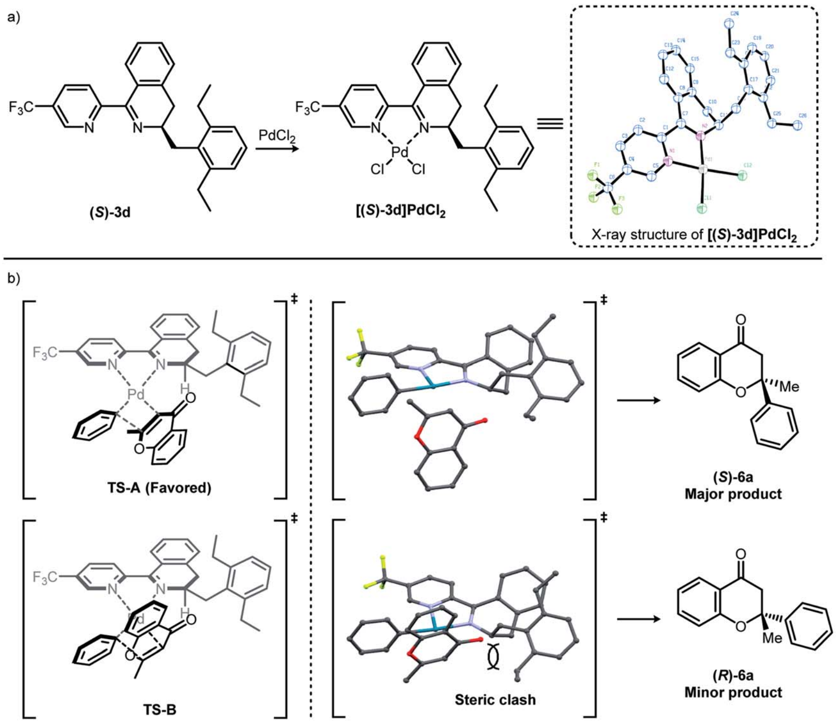


Fig. 1 (a) Synthesis and X-ray structure of [(*S*)-3d]$PdCl_2$ (thermal ellipsoids correspond to 50% probability) and (b) proposed stereochemical model for observed enantioselectivity.

isomeric transition states **TS-A** and **B** (Fig. 1b), **TS-A** leading to the major product, **(*S*)-6a**, might be most favored owing to the minimized steric repulsions between the ligand and the substrate.

Conclusions

In conclusion, new chiral pyridine-dihydroisoquinoline (PyDHIQ) ligands have been developed for the palladium-catalyzed asymmetric conjugate addition reactions in aqueous media. This chemistry represents the first example of a highly enantioselective conjugate addition of arylboronic acids to 2-substituted chromones to afford hindered chromanone products containing tetrasubstituted stereocenters. Twenty-five examples of various arylboronic acids and 2-substituted chromones were demonstrated to provide good isolated yield (31–98%) and outstanding enantioselectivity (90–99%) under the optimized reaction conditions. The observed stereochemistry was rationalized by proposed transition state models. The application of this method to the synthesis of natural products is currently on-going in our laboratories.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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13 The bond length difference between two Pd–Cl bonds is 0.007 Å (see X-ray crystallographic data for [(***S***)-**3d**]$PdCl_2$ in ESI;† Pd–Cl bond length *trans* to dihydroisoquinoline group: 2.287(2) Å, Pd–Cl bond length *cis* to dihydroisoquinoline group: 2.280(2) Å). This value is similar to the bond length difference between two Pd–Cl bonds of [(***S***)-***t*-BuPyOx**]$PdCl_2$ complex (0.009 Å) reported by Jung group (Pd–Cl bond length *trans* to oxazoline group: 2.283(2) Å, Pd–Cl bond length *cis* to oxazoline group: 2.274(2) Å); K. S. Yoo, C. P. Park, C. H. Yoon, S. Sakaguchi, J. O'Neill and K. W. Jung, *Org. Lett.*, 2007, **9**, 3933–3935.