

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.

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

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).

## As featured in:



See Brian M. Stoltz,  
Sukwon Hong *et al.*,  
*Chem. Sci.*, 2020, **11**, 4602.



Cite this: *Chem. Sci.*, 2020, **11**, 4602

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 22nd January 2020  
Accepted 7th April 2020

DOI: 10.1039/d0sc00412j  
[rsc.li/chemical-science](http://rsc.li/chemical-science)

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

Doohyun Baek, <sup>a</sup> Huijeong Ryu, <sup>a</sup> Ji Yeon Ryu, <sup>b</sup> Junseong Lee, <sup>b</sup> Brian M. Stoltz <sup>\*c</sup> and Sukwon Hong <sup>\*ad</sup>

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).<sup>1</sup> Chiral chromanones have been synthesized by various methods,<sup>2</sup> such as intramolecular oxa-Michael additions,<sup>3</sup> asymmetric conjugate additions,<sup>4</sup> asymmetric reductions,<sup>5</sup> and Mitsunobu cyclizations.<sup>6</sup> 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.<sup>7</sup> 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.

<sup>a</sup>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

<sup>b</sup>Department of Chemistry, Chonnam National University, 77 Yongbong-ro, Buk-gu, Gwangju 61186, Republic of Korea

<sup>c</sup>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

<sup>d</sup>School of Materials Science and Engineering, Gwangju Institute of Science and Technology, 123 Cheomdan-gwagiro, Buk-gu, Gwangju 61005, Republic of Korea

<sup>†</sup> 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

Asymmetric conjugate addition reactions<sup>8</sup> 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<sup>4e,9</sup> catalyzed asymmetric conjugate addition chemistry<sup>4e</sup> (Scheme 1b).

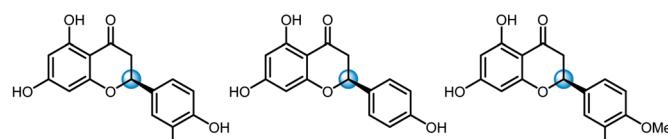
Interestingly, the Stanley group later reported the racemic version of such a conjugate addition of arylboronic acids to 2-substituted chromones catalyzed by a Pd(II)/phenanthroline complex in aqueous media<sup>10</sup> (Scheme 1b). We envisioned that palladium-catalyzed asymmetric conjugate addition 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

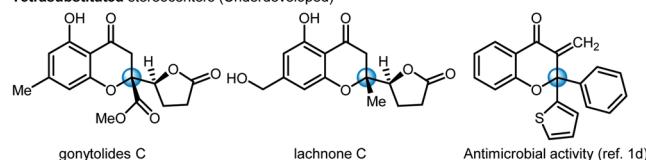
We have previously reported chiral dihydroisoquinoline-based N-heterocyclic carbene (NHC) ligands and (*N,N*) type diimine ligands, which were synthesized *via* Bischler–Napieralski cyclization.<sup>11</sup> Following a similar synthetic protocol, a series of chiral Pyridine-Dihydroisoquinoline (PyDHIQ)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



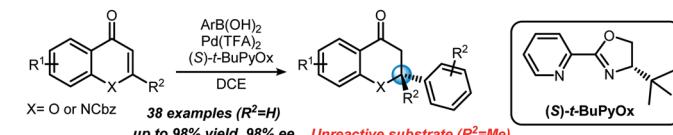
a) Natural products and bioactive compounds containing a stereocenter at C2 position of chromanone  
Trisubstituted stereocenters (Widely developed)



Tetrasubstituted stereocenters (Underdeveloped)



b) Prior art: Pd-catalyzed asymmetric conjugate addition to heterocyclic acceptors  
(Stoltz, 2013)



(Stanley, 2016)



c) This research: Pd-catalyzed asymmetric conjugate addition to 2-substituted chromones



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).

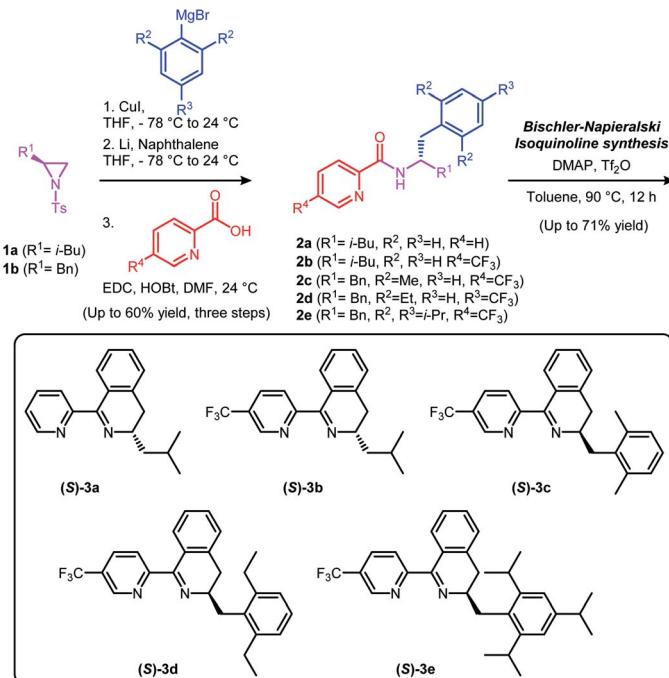
With the chiral PyDHIQ ligands in hand, the asymmetric conjugate addition reaction of phenylboronic acid to 2-methylchromone was investigated by employing the PyDHIQ ligands, Pd(TFA)2, H2O as a solvent, and NH4PF6 as an additive<sup>4e,10</sup> (Table 1).

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 BF4– and PF6– were tested, since these have previously been shown to beneficially impact

the reactivity and selectivity in related conjugate addition reactions.<sup>9b</sup> All the additives tested resulted in better reactivity than without the additive (cf. entries 8–10 with entry 7). PF6– showed higher yields than BF4– (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, NH4PF6 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, O2 atmosphere increased the isolated yield from 33% to 55% at 70 °C (entry 14).<sup>12</sup> Therefore, the optimized reaction conditions including the use of NH4PF6 in O2 atmosphere at 70 °C showed the best combination of reactivity and enantioselectivity.

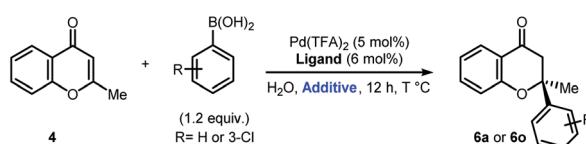
Under the optimized reaction conditions, the substrate scope was examined with various arylboronic acids (Table 2). In case of the reaction with *para*-substituted arylboronic acids, electron-rich boronic acids (Table 2, 6b–6e) resulted in mostly good yields (78–85%) and high enantioselectivity (96–99%),



Scheme 2 Chiral pyridine-dihydroisoquinoline (PyDHIQ) ligands.

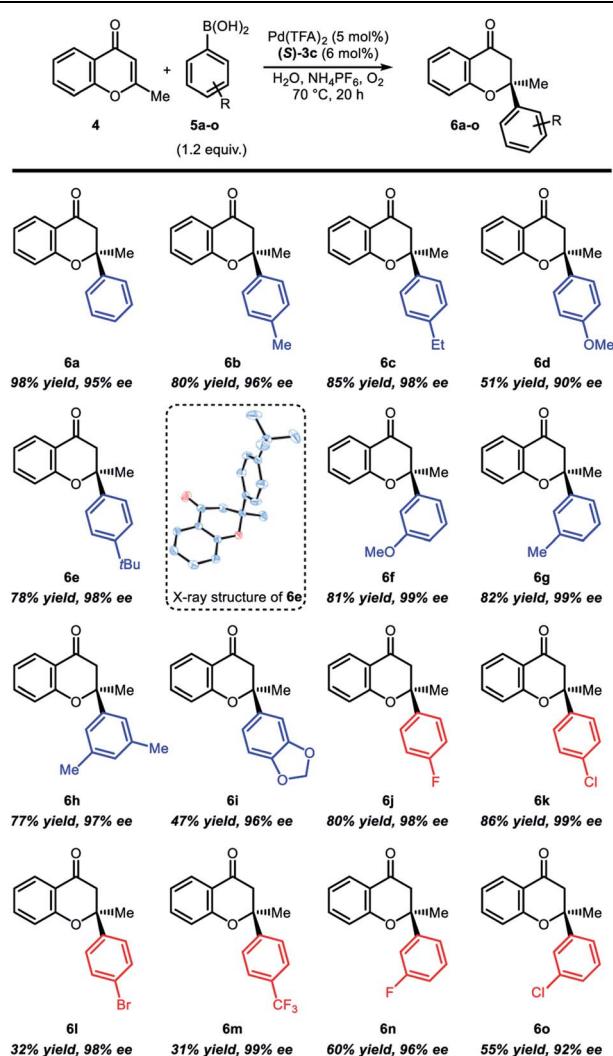
except for *para*-methoxyphenylboronic acid **6d** (51% yields and 90% ee). Reactions with electron-deficient boronic acids such as *para*-fluoro- or *para*-chlorophenylboronic acid also showed good reactivity and high enantioselectivity (Table 2, **6j** and **6k**). However, reduced yields were observed 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<sup>a</sup>

| Entry | T [°C] | ArB(OH) <sub>2</sub>     | Additive (30 mol%)                                       | Ligand                    | Yield <sup>c</sup> [%] | ee <sup>d</sup> [%] |
|-------|--------|--------------------------|--|---------------------------|------------------------|---------------------|
| 1     | 60     | PhB(OH) <sub>2</sub>     | NH <sub>4</sub> PF <sub>6</sub>                          | (S)-t-BuPyOx <sup>b</sup> | Trace                  | —                   |
| 2     | 60     | PhB(OH) <sub>2</sub>     | NH <sub>4</sub> PF <sub>6</sub>                          | (S)-3a                    | Trace                  | —                   |
| 3     | 60     | PhB(OH) <sub>2</sub>     | NH <sub>4</sub> PF <sub>6</sub>                          | (S)-3b                    | 11                     | –68                 |
| 4     | 60     | PhB(OH) <sub>2</sub>     | NH <sub>4</sub> PF <sub>6</sub>                          | (S)-3c                    | 97                     | 95                  |
| 5     | 60     | PhB(OH) <sub>2</sub>     | NH <sub>4</sub> PF <sub>6</sub>                          | (S)-3d                    | 77                     | 98                  |
| 6     | 60     | PhB(OH) <sub>2</sub>     | NH <sub>4</sub> PF <sub>6</sub>                          | (S)-3e                    | 70                     | 98                  |
| 7     | 60     | PhB(OH) <sub>2</sub>     | —  | (S)-3c                    | 42                     | 90                  |
| 8     | 60     | PhB(OH) <sub>2</sub>     | NaBF <sub>4</sub>  | (S)-3c                    | 47                     | 95                  |
| 9     | 60     | PhB(OH) <sub>2</sub>     | NaPF <sub>6</sub>  | (S)-3c                    | 85                     | 95                  |
| 10    | 60     | PhB(OH) <sub>2</sub>     | NH <sub>4</sub> BF <sub>4</sub>                          | (S)-3c                    | 60                     | 90                  |
| 11    | 60     | 3-ClPhB(OH) <sub>2</sub> | NH <sub>4</sub> PF <sub>6</sub>                          | (S)-3c                    | 17                     | 90                  |
| 12    | 70     | 3-ClPhB(OH) <sub>2</sub> | NH <sub>4</sub> PF <sub>6</sub>                          | (S)-3c                    | 33                     | 90                  |
| 13    | 80     | 3-ClPhB(OH) <sub>2</sub> | NH <sub>4</sub> PF <sub>6</sub>                          | (S)-3c                    | 35                     | 89                  |
| 14    | 70     | 3-ClPhB(OH) <sub>2</sub> | NH <sub>4</sub> PF <sub>6</sub> , O <sub>2</sub> balloon | (S)-3c                    | 55                     | 92                  |

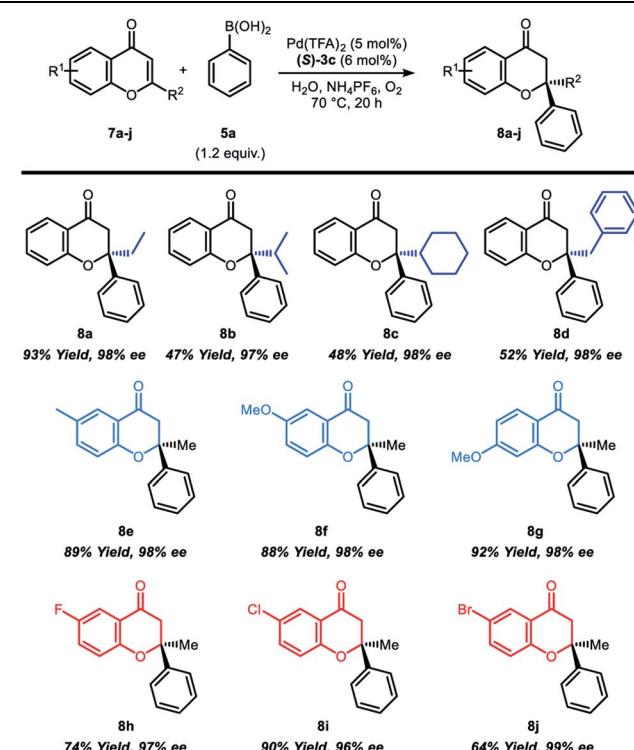
<sup>a</sup> All reactions were carried out with **4** (0.5 mmol, 1 equiv.), ArB(OH)<sub>2</sub> (0.6 mmol, 1.2 equiv.), Pd(TFA)<sub>2</sub> (0.025 mmol, 5 mol%), ligand (0.030 mmol, 6 mol%), additive (0.15 mmol, 30 mol%), H<sub>2</sub>O (0.35 mL) for 12 h. <sup>b</sup> (S)-5-CF<sub>3</sub>-t-BuPyOx also showed trace amount of products; see ESI for additional screening data. <sup>c</sup> Isolated yield of **6a** or **6o**. <sup>d</sup> Determined by HPLC with DAICEL chiralpak.

Table 2 Reaction scope of arylboronic acid nucleophiles<sup>a,b</sup>

<sup>a</sup> All reactions were carried out in vial charged with **4** (0.5 mmol, 1 equiv.), ArB(OH)<sub>2</sub> (0.6 mmol, 1.2 equiv.), Pd(TFA)<sub>2</sub> (0.025 mmol, 5 mol%), (S)-3c (0.030 mmol, 6 mol%), NH<sub>4</sub>PF<sub>6</sub> (0.15 mmol, 30 mol%), H<sub>2</sub>O (0.70 mL), and O<sub>2</sub> balloon for 20 h. <sup>b</sup> 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<sup>5b</sup> 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

Table 3 Reaction scope of chromone electrophiles<sup>a,b</sup>

<sup>a</sup> All reactions were carried out in vial charged with **7** (0.5 mmol, 1 equiv.), PhB(OH)<sub>2</sub> (0.6 mmol, 1.2 equiv.), Pd(TFA)<sub>2</sub> (0.025 mmol, 5 mol%), (S)-3c (0.030 mmol, 6 mol%), NH<sub>4</sub>PF<sub>6</sub> (0.15 mmol, 30 mol%), H<sub>2</sub>O (0.70 mL), and O<sub>2</sub> balloon for 20 h. <sup>b</sup> Isolated yield.

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<sub>2</sub> 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).<sup>13</sup> 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).<sup>9b,9g,12b,13</sup> 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.<sup>9b</sup> Among the two possible



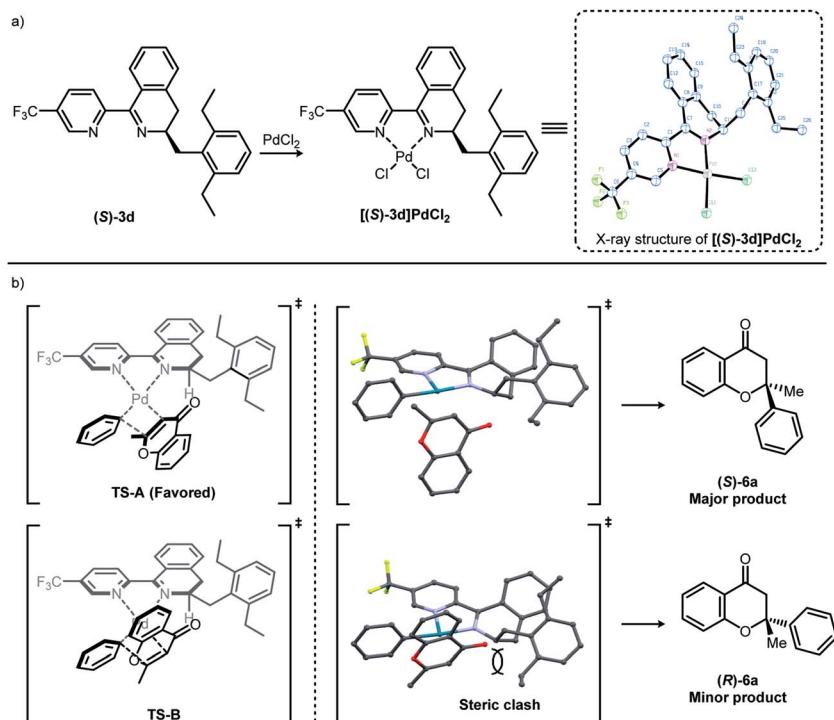


Fig. 1 (a) Synthesis and X-ray structure of  $[(S)-3d]PdCl_2$  (thermal ellipsoids correspond to 50% probability) and (b) proposed stereochemical model for observed enantioselectivity.

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 (Py-DHIQ) 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

This research was supported by the “GIST-Caltech Research Collaboration” grant funded by the GIST in 2017. This research

was also supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (Ministry of Science and ICT) (NRF-2020R1A2C1009123). The NIH-NIGMS (R01GM080269) and Caltech are also thanked for support of our research program.

## Notes and references

- (a) L. C. Chang and A. D. Kinghorn, *Bioactive compounds from natural sources: isolation, characterization and biological properties*, Taylor & Francis, London, 2001; (b) R. J. Grayer and N. C. Veitch, *Flavonoids: Chemistry, Biochemistry and Applications*, CRC, Taylor & Francis, Boca Raton, FL, 2006; (c) S. Emami and Z. Ghanbarimasisir, *Eur. J. Med. Chem.*, 2015, **93**, 539–563; (d) F. E. Ward, D. L. Garling and R. T. Buckler, *J. Med. Chem.*, 1981, **24**, 1073–1077.
- For general reviews, see; (a) A. E. Nibbs and K. A. Scheidt, *Eur. J. Org. Chem.*, 2012, 449–462; (b) L. Meng and J. Wang, *Synlett*, 2016, **27**, 656–663 for other reported researches to synthesize chiral chromaones, see; (c) Z. Zhang, C. Pan and Z. Wang, *Chem. Commun.*, 2007, 4686–4688; (d) C. Wu, Y. Liu, H. Zeng, L. Liu, D. Wang and Y. Chen, *Org. Biomol. Chem.*, 2011, **9**, 253–256; (e) N.-J. Zhong, L. Liu, D. Wang and Y.-J. Chen, *Chem. Commun.*, 2013, **49**, 3697–3699; (f) G. Wen, Y. Su, G. Zhang, Q. Lin, Y. Zhu, Q. Zhang and X. Fang, *Org. Lett.*, 2016, **18**, 3980–3983; (g) A. M. Hardman-Baldwin, M. D. Visco, J. M. Wieting, C. Stern, S.-I. Kondo and A. E. Mattson, *Org. Lett.*, 2016, **18**, 3766–3769; (h) L. G. DeRatt, M. Pappopula and A. Aponick, *Angew.*

*Chem., Int. Ed.*, 2019, **58**, 8416–8420 for kinetic resolution approaches, see; (i) E. J. Corey and R. B. Mitra, *J. Am. Chem. Soc.*, 1962, **84**, 2938–2941; (j) T. L. No, P. Press and G. Britain, *Tetrahedron Lett.*, 1970, 2305–2308; (k) A. Keßberg and P. Metz, *Angew. Chem., Int. Ed.*, 2016, **55**, 1160–1163; (l) E. R. Ashley, E. C. Sherer, B. Pio, R. K. Orr and R. T. Ruck, *ACS Catal.*, 2017, **7**, 1446–1451.

3 (a) M. M. Biddle, M. Lin and K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 3830–3831; (b) C. Dittmer, G. Raabe and L. Hintermann, *Eur. J. Org. Chem.*, 2007, 5886–5898; (c) L. Wang, X. Liu, Z. Dong, X. Fu and X. Feng, *Angew. Chem., Int. Ed.*, 2008, **47**, 8670–8673; (d) H.-F. Wang, H.-F. Cui, Z. Chai, P. Li, C.-W. Zheng, Y.-Q. Yang and G. Zhao, *Chem.-Eur. J.*, 2009, **15**, 13299–13303; (e) H. F. Wang, H. Xiao, X. W. Wang and G. Zhao, *Tetrahedron*, 2011, **67**, 5389–5394; (f) L. Hintermann and C. Dittmer, *Eur. J. Org. Chem.*, 2012, 5573–5584; (g) Y.-L. Zhang and Y.-Q. Wang, *Tetrahedron Lett.*, 2014, **55**, 3255–3258; (h) B. R. McDonald, A. E. Nibbs and K. A. Scheidt, *Org. Lett.*, 2015, **17**, 98–101; (i) M. Shaikh, K. K. Atyam, M. Sahu and K. V. S. Ranganath, *Chem. Commun.*, 2017, **53**, 6029–6032.

4 (a) M. K. Brown, S. J. Degrado and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2005, **44**, 5306–5310; (b) J. Chen, J. Chen, F. Lang, X. Zhang, L. Cun, J. Zhu, J. Deng and J. Liao, *J. Am. Chem. Soc.*, 2010, **132**, 4552–4553; (c) F. Han, G. Chen, X. Zhang and J. Liao, *Eur. J. Org. Chem.*, 2011, 2928–2931; (d) T. Korenaga, K. Hayashi, Y. Akaki, R. Maenishi and T. Sakai, *Org. Lett.*, 2011, **13**, 2022–2025; (e) J. C. Holder, A. N. Marziale, M. Gatti, B. Mao and B. M. Stoltz, *Chem.-Eur. J.*, 2013, **19**, 74–77; (f) C. Vila, V. Hornillos, M. Fañanás-Mastral and B. L. Feringa, *Chem. Commun.*, 2013, **49**, 5933–5935; (g) Q. He, C. M. So, Z. Bian, T. Hayashi and J. Wang, *Chem.-Asian J.*, 2015, **10**, 540–543; (h) B. M. Trost, E. Gnanamani, C. A. Kalnimals, C.-I. Hung and J. S. Tracy, *J. Am. Chem. Soc.*, 2019, **141**, 1489–1493.

5 (a) M.-K. Lemke, P. Schwab, P. Fischer, S. Tischer, M. Witt, L. Noehringer, V. Rogachev, A. Jäger, O. Kataeva, R. Fröhlich and P. Metz, *Angew. Chem., Int. Ed.*, 2013, **52**, 11651–11655; (b) D. Zhao, B. Beiring and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 8454–8458; (c) D. Xiong, W. Zhou, Z. Lu, S. Zeng and J. Wang, *Chem. Commun.*, 2017, **53**, 6844–6847; (d) Y. Ma, J. Li, J. Ye, D. Liu and W. Zhang, *Chem. Commun.*, 2018, **54**, 13571–13574.

6 (a) K. J. Hodgetts, *Tetrahedron Lett.*, 2001, **42**, 3763–3766; (b) Y. Noda and M. Watanabe, *Helv. Chim. Acta*, 2002, **85**, 3473–3477; (c) K. J. Hodgetts, *Tetrahedron*, 2005, **61**, 6860–6870.

7 R. D. Carpenter, J. C. Fettinger, K. S. Lam and M. J. Kurth, *Angew. Chem., Int. Ed.*, 2008, **47**, 6407–6410.

8 For general reviews, see; (a) J. Christoffers, G. Koripelly, A. Rosiak and M. Rössle, *Synthesis*, 2007, **9**, 1279–1300; (b) C. Hawner and A. Alexakis, *Chem. Commun.*, 2010, **46**, 7295–7306; (c) K. Zheng, X. Liu and X. Feng, *Chem. Rev.*, 2018, **118**, 7586–7656.

9 For reported examples on asymmetric conjugate addition reactions by Stoltz group with Pd(II)/PyOx system; (a) K. Kikushima, J. C. Holder, M. Gatti and B. M. Stoltz, *J. Am. Chem. Soc.*, 2011, **133**, 6902–6905; (b) J. C. Holder, L. Zou, A. N. Marziale, P. Liu, Y. Lan, M. Gatti, K. Kikushima, K. N. Houk and B. M. Stoltz, *J. Am. Chem. Soc.*, 2013, **135**, 14996–15007; (c) C. L. Boeser, J. C. Holder, B. L. H. Taylor, K. N. Houk, B. M. Stoltz and R. N. Zare, *Chem. Sci.*, 2015, **6**, 1917–1922; (d) J. C. Holder, E. D. Goodman, K. Kikushima, M. Gatti, A. N. Marziale and B. M. Stoltz, *Tetrahedron*, 2015, **71**, 5781–5792; (e) S. E. Shockley, J. C. Holder and B. M. Stoltz, *Org. Process Res. Dev.*, 2015, **19**, 974–981 see also selected examples on redox-relay oxidative Heck reactions by Sigman using similar Pd(II)/PyOx system; (f) M. S. Sigman, E. W. Werner, T.-s. Mei and A. J. Burckle, *J. Am. Chem. Soc.*, 2013, **135**, 6830–6833; (g) L. Xu, M. J. Hilton, X. Zhang, P.-O. Norrby, Y.-D. Wu, M. S. Sigman and O. Wiest, *J. Am. Chem. Soc.*, 2014, **136**, 1960–1967; (h) T.-S. Mei, H. H. Patel and M. S. Sigman, *Nature*, 2014, **508**, 340–344; (i) M. J. Hilton, L.-P. Xu, P.-O. Norrby, Y.-D. Wu, O. Wiest and M. S. Sigman, *J. Org. Chem.*, 2014, **79**, 11841–11850; (j) C. Zhang, C. B. Santiago, L. Kou and M. S. Sigman, *J. Am. Chem. Soc.*, 2015, **137**, 7290–7293; (k) Z.-M. Chen, M. J. Hilton and M. S. Sigman, *J. Am. Chem. Soc.*, 2016, **138**, 11461–11464 see also a general review of dinitrogen type ligands; (l) G. Yang and W. Zhang, *Chem. Soc. Rev.*, 2018, **47**, 1783–1810.

10 A. L. Gerten and L. M. Stanley, *Tetrahedron Lett.*, 2016, **57**, 5460–5463.

11 (a) H. Seo, D. Hirsch-Weil, K. A. Abboud and S. Hong, *J. Org. Chem.*, 2008, **73**, 1983–1986; (b) D. Hirsch-Weil, K. A. Abboud and S. Hong, *Chem. Commun.*, 2010, **46**, 7525–7527; (c) M. J. Rodig, H. Seo, D. Hirsch-Weil, K. A. Abboud and S. Hong, *Tetrahedron: Asymmetry*, 2011, **22**, 1097–1102.

12 During the reaction optimization, an undesired homocoupling reaction of arylboronic acids was observed. Generation of Pd-black was also observed. Thus, we envisioned that Pd(0) could be reoxidized to Pd(II) in oxygen atmosphere. There are reported examples on oxidation of Pd(0) to Pd(II) using molecular oxygen. A general review for Pd(II)-catalyzed enantioselective oxidative Heck-coupling; (a) A.-L. Lee, *Org. Biomol. Chem.*, 2016, **14**, 5357–5366 a reported example of enantioselective conjugate addition reaction enhanced by introducing molecular oxygen; (b) C. J. C. Lamb, F. Vilela and A.-L. Lee, *Org. Lett.*, 2019, **21**, 8689–8694.

13 The bond length difference between two Pd–Cl bonds is 0.007 Å (see X-ray crystallographic data for [(S)-3d]PdCl<sub>2</sub> 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<sub>2</sub> 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.

