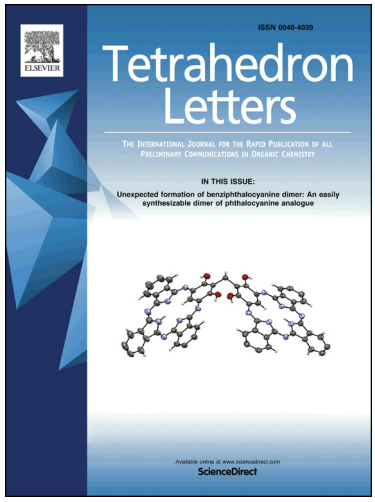

Design and synthesis of chiral 1,10-phenanthroline ligand, and application in palladium catalyzed asymmetric 1,4-addition reactions

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Design and synthesis of chiral 1,10-phenanthroline ligand, and application in palladium catalyzed asymmetric 1,4-addition reactions

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ABSTRACT

Pd-catalyzed asymmetric 1,4-addition of phenylboronic acid to α,β-unsaturated carbonyl compounds was developed using chiral 1,10-phenanthroline derivative as ligand. Good yields (up to 97%), and high enantioselectivities (up to 97% ee) were achieved.

1. Introduction

Transition metal-catalyzed asymmetric reactions are a very important area of organic synthesis research and its focus has been on the design and synthesis of highly efficient chiral ligands as keys to obtaining highly reactivity and enantioselectivity. Through careful fine-tuning of steric and electronic properties, a chiral ligand's coordination with a metal center can easily be modulated, so as to create a chiral environment within the metal-ligand complex that favors the formation of highly reactivity and enantioselectivity in a given reaction.[1]

The use of nitrogen-based chiral ligands has become extremely popular in asymmetric metal catalysis, which is based on efficient and well-documented coordination to late-transition metals. Prominent examples in this respect include chiral semicorrins,[2], bisoxazolines,[3], pyridine-2,6-bisoxazolines,[4], 2,2'-bipyridines,[5], and quinolone- and pyridine-oxazolines,[6] in addition to various hybrid type ligands,[7] all of which have proven to provide excellent levels of enantioselectivity in various reactions.

1,10-Phenanthroline is also a classic chelating bidentate ligand for transition metal ions. It has played an important role in the development of coordination chemistry and continues to be of considerable interest as a versatile material for organic, inorganic, and supramolecular chemistry.[8] Because of their structural rigidity, and hydrophobicity), 1,10-phenanthroline derivatives and their metal complexes are currently used, in molecular recognition and sensing,[9] DNA/RNA binding/cleavage,[10] molecular self-assembling, etc.[11] Therefore, it is surprising that despite the well-known coordination properties of 1,10-phenanthroline, very few reports have been published on the application of phenanthroline derivatives as chiral ligands for asymmetric catalysis.[12]

In an attempt to design chiral phenanthroline ligands for asymmetric catalysis, we focused on functionalizing the peripheral region of the phenanthroline backbone, leaving the aromaticity and, thus, the planarity of all three rings intact (Figure 1). A notable property of phenanthroline derivatives is their π-electron deficiency, which makes them excellent π-acceptors capable of stabilizing metal ions in lower oxidation states. Moreover, the planar π-system and the three rings rigidify the conformation, which simplifies the prediction of phenanthroline metal complex structure. The chiral system resulting from adding bulky and rigid chiral substituents close to the nitrogen atom of the phenanthroline backbone, could provide a transition state in a well-defined chiral environment. Because fewer reaction intermediates must be taken into account, the rigid structure of the ligand has the advantage of facilitating analysis of ligand-metal-substrate interactions in mechanistic studies.

In this way, our design of the chiral phenanthroline ligand is based upon the modification of the phenanthroline backbone upon annulation with chiral bicyclo[3.3.0]octane framework (Figure 1).[13]

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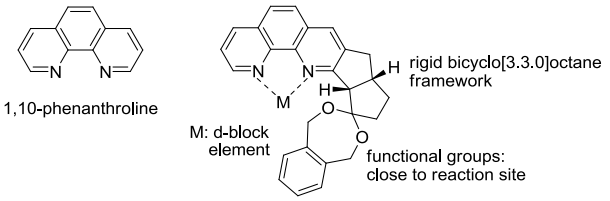


Figure 1. Design of a chiral 1,10-phenanthroline derived ligand.

The chiral bicyclo[3.3.0]octane framework at the stereogenic center is in close proximity to the coordination site, and upon chelation, a substituent on the bicyclo[3.3.0]octane framework could become stereogenic and transmit stereogenic information from the ligand to the metal center. Therefore, substituents on the bicyclo[3.3.0]octane framework are expected to have a strong optical yield direct effect on reactions taking place in the coordination sphere. For this reason, the rigid and planar chiral scaffold of 1,10-phenanthroline-derived chiral ligands have gained considerable attention. We envisaged that this relatively rigid bicyclo[3.3.0]octane moiety could increase the asymmetric induction ability of 1,10-phenanthroline-derived chiral ligands. The ketal can be readily converted back to the ketone functional group by deprotection, and there is possibility the carbonyl group can convert to another functional group. Therefore, the 1,10-phenanthroline-derived chiral ligand is readily modified by variation of the substituents at the bicyclo[3.3.0]octane framework (Figure 1).

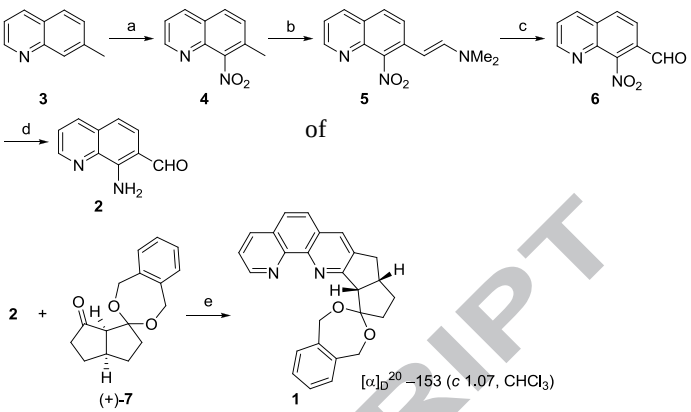
Catalytic asymmetric conjugate addition of C-nucleophiles to α,β-unsaturated carbonyl compounds is a powerful method of synthesizing asymmetric C-C bonds. The combination of rhodium catalysts and organoboronic acids has emerged as a powerful and ideal catalytic system for 1,4-addition.[14] A method of 1,4-addition of organoboronic acids to α,β-unsaturated carbonyl compounds has been developed, and various research groups have reported the use of metals that are less expensive than rhodium.[15] In, 1995, Uemura reported using palladium/$SbCl_3$ to catalyze 1,4-addition to α,β-unsaturated carbonyl compounds, giving racemic products.[16] Miyaura, developed the method of arylboronic acids addition to α,β-unsaturated carbonyl compounds using chiral cationic palladium-phosphine complexes as catalysts.[17] Recently, as an example of using nitrogen-based ligand in palladium-catalyzed asymmetric 1,4-addition reactions, Stoltz and Houk reported a combined experimental and computational investigation on the mechanism of enantioselectivity.[6d-h]

Herein, we report on the development of a method of 1,10-phenanthroline-derived chiral ligand synthesis and the application of this new ligand to the catalytic asymmetric 1,4-addition to α,β-unsaturated carbonyl compounds.

2. Results and Discussions

The studies commenced with the synthesis of the new 1,10-phenanthroline-derived chiral ligand **1**, which was obtained by performing a Friedländer condensation of 8-aminoquinoline-7-carbaldehyde (**2**) with chiral bicyclo[3.3.0]octanone derivative (+)-**7** as shown in Scheme 1.[19]

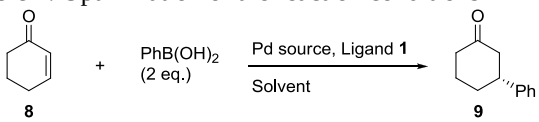
Recently, we have accomplished a practical synthesis of chiral bicyclo[3.3.0]octane derivative (+)-**7** for use as a chiral building block.[13] Synthesis of **2** begins with 7-methylquinoline (**3**), and straightforward nitration produces **4** in excellent yield after recrystallization from hexane–AcOEt. The 7-methyl group can then be functionalized by the Leimgruber-Batcho method with *N*, *N*-dimethylformamide dimethyl acetal (DMFDMA) to provide the corresponding *N*, *N*-dimethylamino alkene **5** according to the previously published procedure.[18] Oxidation of the aminoalkene **5** is accomplished with sodium periodate to provide the *ortho*-nitro aldehyde **6** in good yield. Reduction of the analogous nitro group to amine is carried out with powdered iron. The Friedländer condensation of **2** with chiral bicyclo[3.3.0]octanone derivative (+)-**7** under basic conditions (KOH, EtOH, 90 °C) provides the corresponding 1,10-phenanthroline derived chiral ligand **1** in 53% yield after recrystallization from hexane–benzene.[19]



Scheme 1. Reagents and conditions: (a) *c*.HNO_3, *c*.H_2SO_4, 100 °C, recrystallization from hexane–AcOEt, 72% (b) DMFDMA, DMF, 140 °C, 80% (c) $NaIO_4$, THF/H_2O, r.t., 90% (d) Fe, *c*.HCl, AcOH/EtOH/H_2O, r.t., 86% (e) KOH, EtOH, 90 °C, recrystallization from hexane–benzene

In terms of all the results summarized in Table 1, ligand **1** demonstrated considerable potential for catalytic asymmetric 1,4-addition of $PhB(OH)_2$ to 2-cyclohexen-1-one (**8**) with high activity and enantioselectivity.

Table 1. Optimization of the reaction conditions[a]



Entry	Pd source	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	$Pd(OTf)_2$	$ClCH_2CH_2Cl/H_2O$	60	17	97	94
2	$Pd(OTf)_2$	$ClCH_2CH_2Cl$	60	16	96	91
3	$Pd(OTf)_2$	$ClCH_2CH_2Cl/H_2O$	23	144	n.d.[d]	-
4	$Pd(OTf)_2$	$ClCH_2CH_2Cl/H_2O$	40	17	56	90
5	$Pd(OTf)_2$	CH_3OH	60	48	0	-
6	$Pd(OTf)_2$	DMF/H_2O	60	24	59	81
7	$Pd(OTf)_2$	$toluene/H_2O$	60	24	58	76
8	$PdCl_2$	$ClCH_2CH_2Cl/H_2O$	60	18	0	-
9	$Pd(OAc)_2$	$ClCH_2CH_2Cl/H_2O$	60	16	41	90
10[e]	$Pd(OTf)_2$	$ClCH_2CH_2Cl/H_2O$	60	48	90	91

[a] Reactions were carried out with phenylboronic acid (0.50 mmol), **8** (0.25 mmol), Pd source (5 mol%), ligand **1** (6 mol%) in solvent (1.0 ml), and H_2O (0.1 ml) at the indicated temperature.

[b] Isolated yield.

[c] Determined by HPLC (Chiralcel OD-H) or optical rotation[14].

[d] n.d. = not determined.

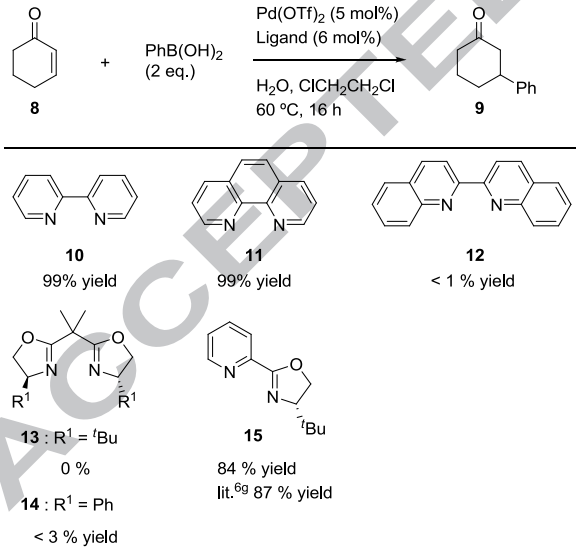
[e] Reaction performed with 1 mol% of catalyst.

Initially, 2-cyclohexen-1-one (**8**) was added to $PhB(OH)_2$ (2.0 eq.) in the presence of 5 mol% $Pd(OTf)_2$, ligand **1** in H_2O (0.1 ml), and $ClCH_2CH_2Cl$ (1.0 ml) at 60 ºC for 17 h, and the desired adduct **9** was readily delivered with 97% yield and 94% ee (Table 1, entry 1).[20] The reaction afforded the desired conjugate addition product without traces of either the 1,2-addition product or the Heck coupling product. On the basis of the above analysis, the effects of solvent and temperature were investigated with **1** as the ligand in the presence of $Pd(OTf)_2$. The reaction requires the presence of water to hydrolyze boroxine[21] and to be an adequate the source of protons for catalyst turnover. However, the reaction occurred in 96% yield in the absence of water, in 97% yield when water was added to the boronic acid (Table 1, entry 2). We speculated that when performed on a small scale, the reaction requires only a small amount of moisture (such as might be present in the reagent and/or on glassware) to proceed to completion.[6f,h]

When the temperature was lowered to 0 ºC, the reaction did not proceed and no product was detected. The reaction can proceed at 40 ºC, but not at 23 ºC for 5 days (Table 1, entry 3, 4). The reaction did not proceed in toluene, donating solvents such as CH_3OH, DMF and proceeded best in $ClCH_2CH_2Cl$ (Table 1, entry 5–7). In addition, we examined other Pd sources such as $PdCl_2$ and $Pd(OAc)_2$. However, the combination of $PdCl_2$, $Pd(OAc)_2$, and ligand **1** did not give good results (Table 1, entry 8, 9). The catalyst loading could be decreased, and on a 1 mmol scale, 90% yield, 91% ee was obtained with 1 mol% of catalyst in 48 h (Table 1, entry 10).

To close the investigation into ligand structure and asymmetric induction of this reaction, the reaction of 2-cyclohexen-1-one (**8**) with $PhB(OH)_2$ was screened in the presence of other bidentate nitrogen ligands under optimized conditions (Table 2).

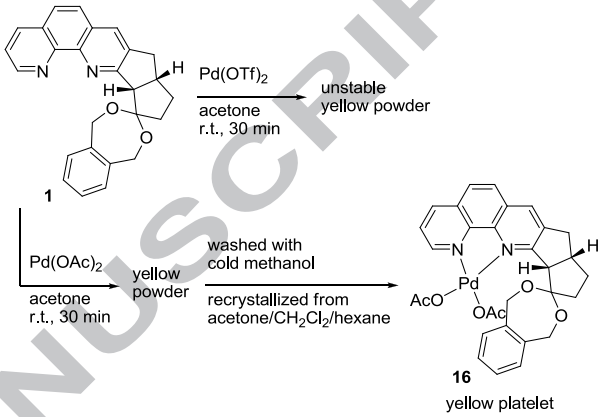
Table 2. Screening of bidentate nitrogen ligands[a]



[a] Reactions were carried out with phenylboronic acid (0.50 mmol), **8** (0.25 mmol), $Pd(OTf)_2$ (5 mol%), and ligand (6 mol%) in $ClCH_2CH_2Cl$ (1.0 ml), H_2O (0.1 ml) at 60 °C for 16 h.

Unfortunately, the chiral bis-oxazoline ligand (**13**, **14**) scaffold failed to afford any conversion to the desired conjugate addition product. The best conversion was observed with ligands having a bite angle similar to that of 2,2'-bipyridine (**10**), 1,10-phenanthroline (**11**) and pyridine-oxazoline ligand (**15**), which also feature a five-membered chelate ring. Increasing the bite angle of the ligand should force the metal closer to the ligand center, and any substrates bound to the metal will then also be brought closer to the substituents on the two oxazolines.[18] Also, when comparing 2,2'-bipyridine (**10**) and 2,2'-biquinoline (**12**), which also features a five-membered chelate ring, both benzene rings of 2,2'-biquinoline (**12**) will move closer to the metal ion. Therefore, we consider that C_2 symmetry phenanthroline ligands are difficult to modify at the metal coordination center in this reaction, and C_1 symmetry chiral ligands on the phenanthroline scaffold would be a suitable catalyst.

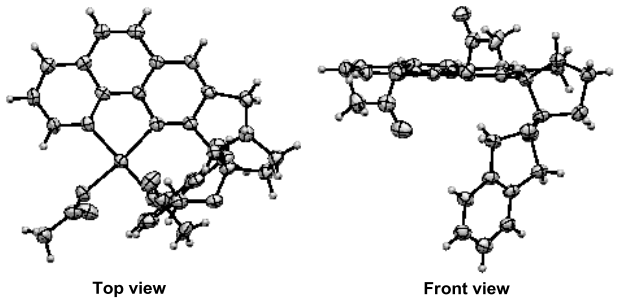
An X-ray crystallographic study is also provided in support of a proposed model for asymmetric induction. Unfortunately, though, as an X-ray crystal structure of the [Pd(ligand **1**)]$(OTf)_2$ complex was not available, so X-ray crystallographic analysis was carried out on a single crystal of [Pd(ligand **1**)]$(OAc)_2$ complex (**16**) (Scheme 2). The [Pd(ligand **1**)]$(OAc)_2$ complex (**16**) was prepared by mixing ligand **1** and $Pd(OAc)_2$ in acetone, followed by a recrystallization from acetone–CH_2Cl_2–hexane.[22]



Scheme 2. Synthesis of [Pd(ligand **1**)]$(OAc)_2$ complex (**16**).

As in Figure 3, an square planar, mononuclear [Pd(ligand **1**)]$(OAc)_2$ complex (**16**) was identified in which ligand **1** coordinate the palladium center in a *cis* topology, affording a C_1-symmetric palladium complex.

Figure 3. The ORTEP diagram of complex (**16**) (thermal ellipsoids



correspond to 50% probability). Noncoordinating molecules have been omitted for clarity (CCDC-1557225).

This stereocontrol model can be applied to predict the absolute configurations of 1,4-addition products with the ligand **1**-Pd intermediate and an X-ray crystallographic study of [Pd(ligand **1**)]$(OAc)_2$ complex (**16**). The stereochemical pathways with ligand **1** are rationalized in Figure 4.

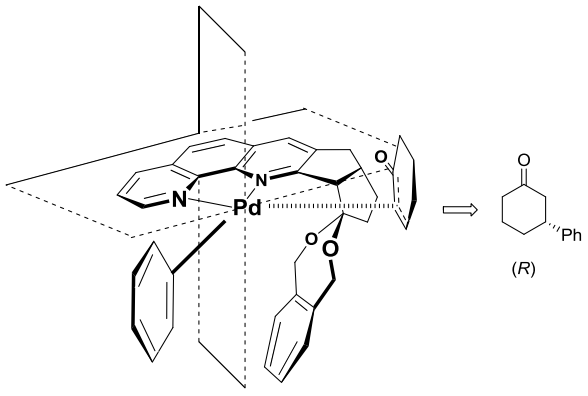
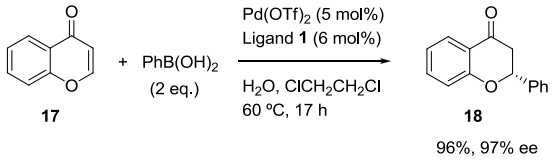


Figure 4. Proposed stereochemical pathway for the 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one (**8**) using ligand **1**.

The conformationally rigid framework of the ligand **1**-Pd intermediate with stereocenters close to the donor nitrogen atoms imposes a well-ordered chiral environment at the catalytic site.

Since the 1,4-addition product of the *R* form was obtained, the transmetalation proceeded so as to avoid steric repulsion between the group on the bicyclo[3.3.0]octane moiety and the phenanthroline skeleton of the ligand **1** -Pd catalyst. Thus, the initial coordination of the Pd catalyst might result in a *trans* relationship between the phenyl group and the bicyclo[3.3.0]octane moiety of the ligand **1**. The ligand **1**-Pd intermediate should have an open space at the first quadrant of the vacant coordination site, because the bicyclo[3.3.0]octane moiety of the ligand **1** blocks the fourth quadrant. The olefinic double bond of 2-cyclohexen-1-one (**8**) coordinates to palladium, in the *Re* face rather than the *Si* face fashion, and the double bond undergoes migratory insertion, leading to a product with *R* absolute configuration.

Finally, we tried to synthesize flavanone (Scheme 3). We reacted chromone (**17**) with $PhB(OH)_2$ using chiral phenanthroline ligand **1**. The reaction gave flavanone (**18**) in 96% yield with 97% ee.[23]



Scheme 3. Asymmetric 1,4-addition of phenylboronic acid to chromone (**17**) using ligand **1**.

3. Conclusion

In summary, we described the synthesis of chiral phenanthroline ligand and found that this chiral phenanthroline was an efficient catalyst for the palladium-catalyzed asymmetric 1,4-addition of phenyl boronic acid to enones with ee up to 97%. Further studies on substrate and boronic acid scope, the development of efficient ligands are in progress.

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19. Preparation of (3'a'*S*,6'a'*S*)-(hexahydro-2''*H*-spiro[1'',5''-dihydro-2'',4''-benzodioxepin-3'',6'-pentalenyl])-[1,2-*b*]-1,10-phenanthroline (**1**)
Into a 50 ml sealed tube, equipped with magnetic stirrer under an atmosphere of argon was introduced a mixture of 8-aminoquinoline-7-carbaldehyde (**2**) (500 mg, 2.9 mmol), (+)-**7** (750 mg, 2.9 mmol), and saturated ethanolic KOH (120 mg) in absolute EtOH (4.0 ml), and the solution was 90 °C for 16 h. The course of the reaction was followed by TLC on SiO_2 eluting with 10:1 CH_2Cl_2/MeOH (R_f = 0.45). After cooling, the mixture partitioned between CH_2Cl_2 and water. The combined organic phases were washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by SiO_2 column chromatography (SiO_2, 20:1 CH_2Cl_2/MeOH) to afford the title compound **1** (743 mg, 65%). Recrystallization from hexane/benzene provided **1** as a white solid; mp. 140-141 °C, TLC R_f = 0.45 (10:1 CH_2Cl_2/MeOH); $[\alpha]_D^{20}$ -153 (*c* 1.07, $CHCl_3$); IR (film) 2975, 2870, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.65-1.90 (m, 2H, C5'-*H*), 2.19-2.24 (m, 2H, C6'-*H*), 3.01-3.07 (dd, *J* = 1.4, 16.9 Hz, 1H, C3'-*H*), 3.35-3.39 (m, 1H, C4'-*H*), 3.46-3.53 (dd, *J* = 9.8, 16.9 Hz, 1H, C3'-*H*), 4.23 (d, *J* = 8.8 Hz, 1H, C7'-*H*), 5.06 (dd, *J* =2.3, 14.8 Hz, 2H, OC*H*$_2$Ar), 5.42 (d, *J* = 14.8 Hz, 1H, OC*H*$_2$Ar), 5.63 (d, *J* = 15.3 Hz, 1H, OC*H*$_2$Ar), 7.10-7.19 (m, 4H, Ar*H*), 7.57 (dd, *J* = 4.3, 8.1 Hz, 1H, phenanthroline*H*), 7.73 (d, *J* = 8.8 Hz, 2H, phenanthroline*H*), 7.97 (s, 1H, phenanthroline*H*), 8.20 (dd, *J* = 1.8, 8.1 Hz, 1H, phenanthroline*H*) , 9.16 (dd, *J* = 1.8, 4.3 Hz, 1H, phenanthroline*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2 (CH_2), 32.2 (CH_2), 37.9 (CH_2), 39.7 (CH), 58.8 (CH), 66.3 (CH_2), 68.4 (CH_2), 114.5 (C), 122.1 (CH), 125.5 (CH), 125.6 (CH), 125.8 (CH), 126.4 (CH), 126.6 (CH), 126.7 (CH), 127.9 (C), 128.1 (C), 131.0 (CH), 135.8 (CH), 138.1 (C), 138.1 (C), 138.2 (C), 145.8 (C), 146.3 (C), 150.8 (CH), 164.6 (C); EI-HRMS *m*/*z* calcd. for $C_{26}H_{22}N_2O_2$ (M^+) 394.1681, found 394.1488.

20. The typical experiment for the 1,4-addition of phenyl boronic acid to 2-cyclohexen-1-one (**8**):
A Schlenk tube was charged with stir bar, $Pd(OTf)_2$ (4.2 mg, 0.0125 mmol), ligand **1** (5.9 mg, 0.015 mmol), and the solids were dissolved in $ClCH_2CH_2Cl$ (1.0 ml), H_2O (0.1 ml) and the solution was flushed with argon. After the yellow solution stirred for 5 min at ambient temperature, phenyl boronic acid (61 mg, 0.5 mmol) was added and followed by addition of 2-cyclohexen-1-one (**8**) (24 mg, 0.25 mmol). The resulting mixture was then stirred at 60 °C in an oil bath for 16 h. Upon complete consumption of the starting material (monitored by TLC, 5:1 hexane/EtOAc) the reaction mixture was eluted through short column of SiO_2, using AcOEt as the eluent, and concentrated in vacuo. The crude residue was purified by chromatography (SiO_2, 10:1 hexane/AcOEt) to provide the 3-phenylcyclohexanone (**9**) as colorless oil (39.8 mg, 0.23 mmol). The enantiomeric ratio was determined by HPLC using a chiral column (Daisel Chiralcel OD-H), hexane/2-propanol 98:2, 0.5 ml/min, 254 nm, 29.7 min (minor), 30.7 min (major).

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22. CCDC-1557225 [for [Pd(ligand 1)]$(OAc)_2$ complex (**16**)] contain the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallograohic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

23. The typical experiment for the 1,4-addition of phenyl boronic acid to chromone (**17**):
A Schlenk tube was charged with stir bar, $Pd(OTf)_2$ (4.2 mg, 0.0125 mmol), ligand **1** (5.9 mg, 0.015 mmol), and the solids were dissolved in $ClCH_2CH_2Cl$ (1.0 ml), H_2O (0.1 ml) and the solution was flushed with argon. After the yellow solution stirred for 5 min at ambient temperature, phenyl boronic acid (61 mg, 0.5 mmol) was added and followed by addition of chromone (**17**) (36.5 mg, 0.25 mmol). The resulting mixture was then stirred at 60 °C in an oil bath for 17 h. Upon complete consumption of the starting material (monitored by TLC, 5:1 hexane/EtOAc) the reaction mixture was eluted through short column of SiO_2, using AcOEt as the eluent, and concentrated in vacuo. The crude residue was purified by chromatography (SiO_2, 10:1 hexane/AcOEt) to provide the flavanone (**18**) as white solid (53.8 mg, 0.24 mmol). The enantiomeric ratio was determined by HPLC using a chiral column (Daisel Chiralcel OD-H), hexane/2-propanol 9:1, 1.0 ml/min, 254 nm, 8.4 min (minor), 10.1 min (major).

Research highlights

- Design and synthesis of rigid 1,10-phenanthroline-derived chiral ligand.
- New ligand demonstrated potential for catalytic 1,4-addition with high enantioselectivity.
- This stereocontrol model can be applied to predict an X-ray crystallographic study.

Graphical Abstract

Design and synthesis of chiral 1,10-phenanthroline ligand, and application in palladium catalyzed asymmetric 1,4-addition reactions

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