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Breaking Report

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Catalytic Enantioselective Construction of 6-4 Ring-Junction All-Carbon Stereocenters and Mechanistic Insights

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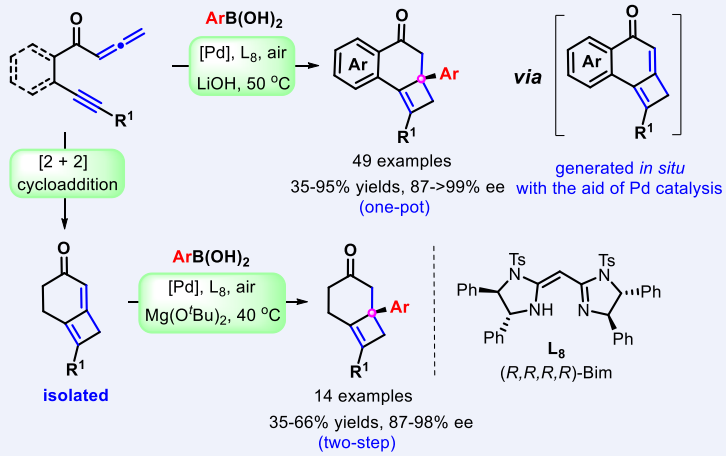
Comprehensive Summary

Developing reactions for the synthesis of 6-6-4 and 6-4 carbocyclic scaffolds with a chiral quaternary center at the bridgehead position is highly desired, considering the existence of such skeletons in natural products with biological activities and the potential of using these molecules for downstream studies in chemical biology and medicinal chemistry. Report here is accessing these target skeletons with high chemo-, regio- and enantio-selectivities through Pd(II)/chiral *N*,*N*′-disulfonyl bisimidazoline (Bim) ligand-catalyzed asymmetric reaction of yne-allenones and arylboronic acids. Realization of 6-6-4 skeleton with a ring-junction all-carbon stereocenter is a one-step process while synthesizing 6-4 skeleton is a two-step process, which begins with intramolecular [2 + 2] reaction of allenes with alkynes, followed by Pd-catalyzed asymmetric addition of arylboronic acids to cyclic enones generated in the first step. Noteworthy is that chiral Bim ligand as a C_2-symmetric *N*,*N*′-bidentateanionic ligand, designed by us, in coordinating with Pd catalyst was first applied to catalyze asymmetric 1,4-conjugate addition reaction with the high catalytic performance (the reaction can be carried out in air). DFT calculations have been applied to understand how these reactions take place, the origins of enantioselectivity, and relative reactivities of different substrates.



Keywords

Asymmetric catalysis | Palladium | Michael addition | Chiral cyclobutenes | Mechanism

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Background and Originality Content

Developing new reactions and strategies to construct various molecular skeletons is one of the most impacting frontiers of organic synthesis, considering that advances in this direction will improve efficiency in accessing natural products and analogs with various rings, substituents and stereochemistry.[1] This is also important to advance pharmaceutical chemistry because the new skeletons developed, whether they are found in nature or not, will expand the chemical space of drug discovery and other fields as well. In line with these, we think that developing reactions for the synthesis of 6-6-4 and 6-4 small-sized carbocyclic scaffolds with a chiral quaternary center at the bridgehead position is a required technology.[2] This can be understood, on one hand, by the existence of such skeleton in natural products with biological activities, exemplified by 6β-acetoxy-13α-hydroxyhaplopan-7-one,[3] cornutin L,[4] sterpurene,[5] illudiolone,[6] and atlanticone C[7] (Figure 1), and on the other hand, by the potential of using these molecules for downstream studies in chemical biology and medicinal chemistry. Unfortunately, synthesizing this skeleton faces several challenges such as overcoming ring-strain of forming four-membered rings[8] and steric congestion of building quaternary stereocenters[9] and control of the stereochemistry.

Despite these challenges, a few asymmetric methods for the construction of 6-4 carbocyclic scaffolds with ring-junction all-carbon stereocenters are documented. A common asymmetric strategy for creating 6-4 carbocyclic ring adopts chirality transfer using intramolecular [2 + 2] cycloaddition of β,γ-alkynyl ketones catalyzed by chiral thiourea catalyst (Figure 1b, Brown's work).[10] An alternative route relies on intermolecular [2 + 2] photocycloaddition reaction between cyclic enones and alkenes under rigorously cryogenic conditions (Figure 1b, Bath's work).[11] Further development of a versatile catalytic strategy that performs with high efficiency and selectivity under mild conditions would be a major advance for the enantioselective construction of these useful, highly strained 6-6-4 and 6-4 skeletons associated with a chiral quaternary center at the ring-junction position.

Our original idea to reach the 6-4 ring-junction all-carbon stereocenters for both 6-6-4 and 6-4 skeletons is to apply [2 + 2] cycloaddition reaction of yne-allenones to build 6-4 cyclic skeleton **A**,[12] which then can be converted to the final target product **I** by applying metal-catalyzed conjugate 1,4-addition of arylboronic acids.[13] Here are the possible challenges (Figure 1c): 1) we were not sure whether the 6-4 cyclic intermediate **A** can or cannot be

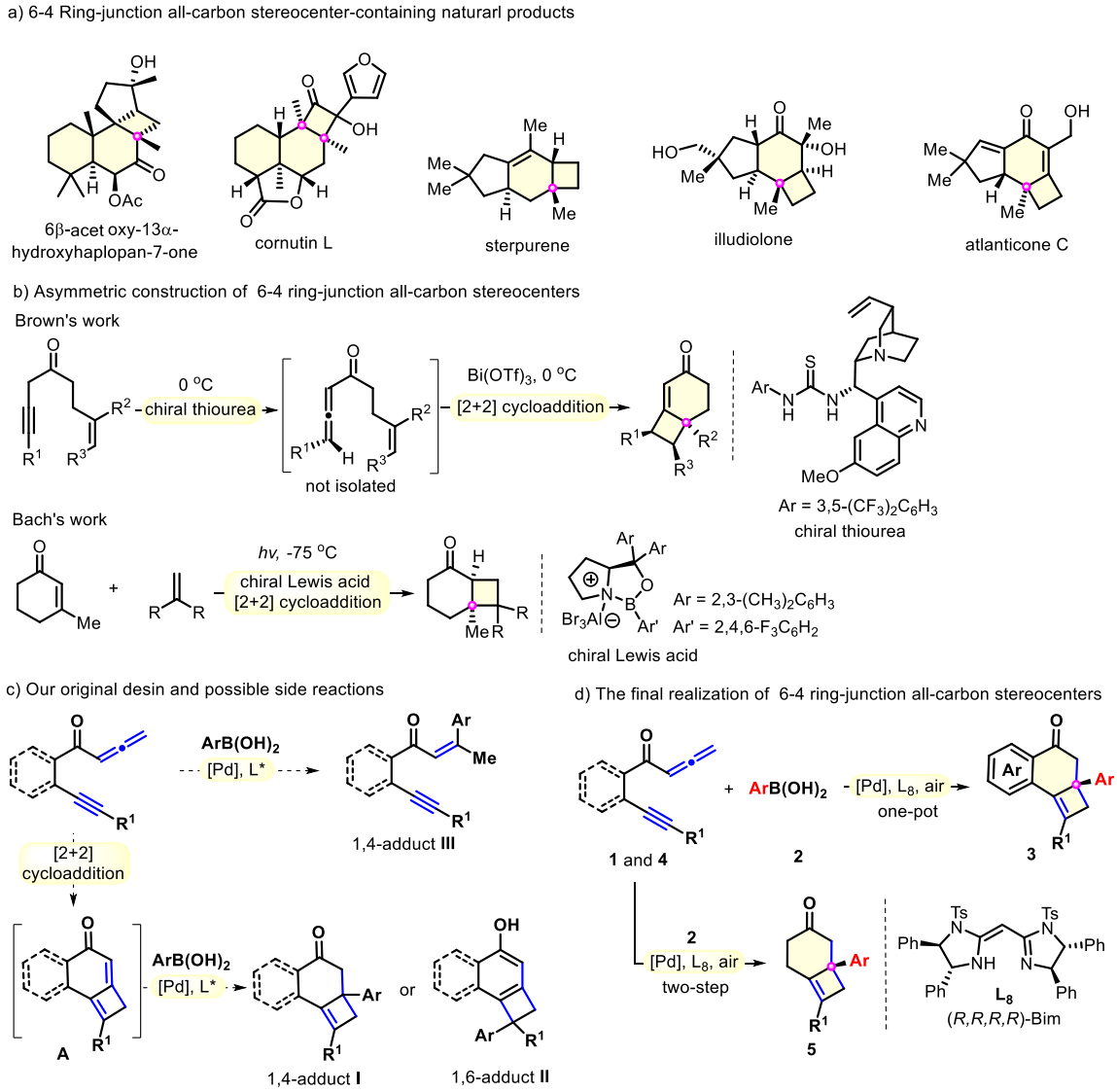


Figure 1 Natural products and catalytic enantioselective construction of 6-4 ring-junction all-carbon stereocenters.

generated, considering its high strain in the four membered ring; 2) 1,4-addition step is possible or not. Actually, such addition can be catalyzed by Rh or Pd, but none of them have been tested for enones in 6-4 cyclic system;[14] 3) a side reaction could be favored to give product **II** through 1,6-addition;[15] 4) we also wanted to test in one-pot synthesis of target molecules without involving intermediate **A**, but such a reaction could face the generation of side product **III**, formed by a direct 1,4 addition/alkene isomerization; 5) if all of the above challenges can be resolved, can this be extended to its asymmetric version?

Here, we report our achievement to realize the final goals by carrying out a Pd(II)/chiral *N*,*N*′-disulfonyl bisimidazoline (Bim) ligand-catalyzed asymmetric reaction of yne-allenones and arylboronic acids. Specifically, Pd(II)/Bim-catalyzed reaction of benzene-linked yne-allenones **1** with arylboronic acids **2** resulted in 6-6-4 carbocyclic skeletons bearing an all-carbon quaternary stereocenter at the 6-4 ring-junction position with high chemo-, regio- and enantio-selectivities in a one-pot fashion. But when alkyl-tethered yne-allenones **4** with different substituents were employed, the reaction proceeded through a two-step process, delivering the expected enantioenriched bicyclic cyclobutenes **5** with a 6-4 ring-junction all-carbon stereocenter by fine-tuning the base and reaction temperatures (Figure 1d). Noteworthy is that chiral (*R*,*R*,*R*,*R*)-*N*,*N*′-disulfonyl bisimidazoline (Bim) ligand as a C_2-symmetric *N*,*N*′-bidentate anionic ligand[16] that we designed in coordination with Pd catalyst was first applied to catalyze asymmetric 1,4-conjugate addition reaction with the high catalytic performance.[17] Intrigued by excellent enantioselective control of this Bim ligand and the wide substrate scope of asymmetric reaction, we have also performed systematic theoretical calculations to elucidate the reaction mechanism, origins of enantioselectivity and reactivities of different substrates (see the mechanism section and Supporting Information).

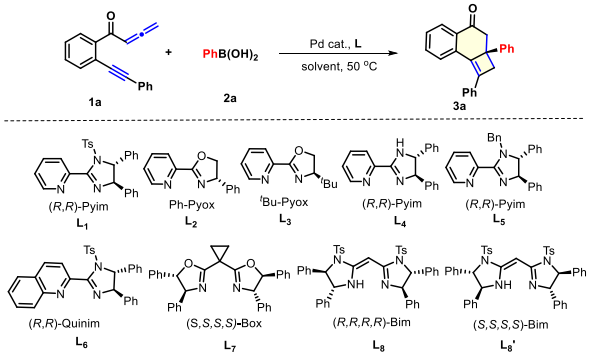
Results and Discussion

Initial test of reaction conditions

We tested our idea by firstly trying a one-pot reaction of yne-allenone **1a** with phenylboronic acid (**2a**) (**L**$_1$, (*R*,*R*)-*N*-Ts-Pyim)[18] for the synthesis of 6-6-4 tricyclic product **3a**. We examined this in DCE solvent in the presence of $Pd(OCOCF_3)_2$ and chiral *N*-tosyl 2-(2-pyridyl)imidazoline at 50 °C in air. To our delight, the target product **3a** was generated in 72% yield and 79% ee (Table 1, entry 1). Decreasing the reaction temperature from 50 °C to 30 °C was not beneficial to the yield of **3a**, with similar enantioselection (entry 2). Further efforts in screening several other solvents, such as CH_3CN, 1,4-dioxane, CH_3CO_2Et, and toluene revealed that all these reaction media gave remarkably dropped yields of **3a**, along with the maintenance of ee values (entries 3—6). Switching the palladium catalyst from $Pd(OCOCF_3)_2$ to $Pd(OAc)_2$ led to the lower conversion of **1a** into **3a** with a slightly decreased ee value (entry 7 vs entry 1). With $Pd(OCOCF_3)_2$ as the catalyst in DCE, the effect of the ligands on the transformation was then investigated. A number of bidentate nitrogen ligands, such as Ph-Pyox **L**$_2$,[19] ^{t}Bu-Pyox **L**$_3$,[14a] free Pyim **L**$_4$,[18] *N*-Bn-Pyim **L**$_5$,[18] *N*-Ts-Quinim **L**$_6$, (*S*,*S*,*S*,*S*)-Box **L**$_7$[20] and (*R*,*R*,*R*,*R*)-*N*,*N*′-disulfonyl Bim **L**$_8$, were next assayed with the aim of increasing the enantioselectivity of this reaction (entries 8—14). Chiral ligands **L**$_2$—**L**$_4$ afforded lower enantioselectivities (entries 8—10), probably because of poor steric hindrance. The introduction of the benzyl group into the nitrogen atom of imidazole ring resulted in a slightly increased yield but remarkably lowered the enantioselectivity of this reaction (entry 11). The use of *N*-Ts-Quinim (**L**$_6$) as the ligand completely suppressed the reaction (entry 12). We were happy to find that, cyclopropyl-linked bisoxazoline **L**$_7$ as a C_2-symmetric chiral ligand[21] showed good asymmetric induction ability (entry 13). This observation prompted us to prepare C_2-symmetric *N*-tosyl protected (*R*,*R*,*R*,*R*)-Bim from commercially available (*R*,*R*)-1,2-diphenylethane-1,2-diamine[22] and employ it as the ligand (**L**$_8$) for this asymmetric addition reaction. The synthesis of this ligand was performed through a simple two-step reaction of (*R*,*R*)-1,2-diphenylethane-1,2-diamine with diethyl malonimidate dihydrochloride followed by sulfonylation with tosyl chloride.[16] Delightedly, this chiral ligand performed well with higher enantioselectivity (entry 14). It is found that the use of appropriate bases dramatically increased the enantioselectivity (entries 15—19), with LiOH giving the highest enantiomeric excess (98% ee) and a good yield (entry 16, the optimal conditions used for substrate scope study). The (*S*,*S*,*S*,*S*)-*N*,*N*′-disulfonyl Bim ligand **L**$_8$' was also examined and showed the similarly excellent enantioselectivity, offering the product **3a** with an opposite configuration in 66% yield (entry 20).

We want to mention here that, in the absence of Pd catalyst, **1a** at room temperature can gradually undergo intramolecular metal-free [2 + 2] reaction of allene toward alkyne to give [2 + 2] cycloadduct **8a**, which can also be utilized to synthesize **3a** using the current conditions when reacted with **2a** under the Pd catalysis (see this in Supporting Information). Even though this two-step process for the synthesis of 6-6-4 product was effective, we preferred to use the one-pot reaction conditions as shown in entry 16, Table 1, which was also applied for all substrates shown below.

Table 1 Optimization of the reaction conditions[a]



Entry	Ligand (mol%)	Base (equiv)	Solvent	Yield[b]/%	ee[c]/%
1	**L**$_1$ (10)	—	DCE	72	79
2[d]	**L**$_1$ (10)	—	DCE	51	78
3	**L**$_1$ (10)	—	CH_3CN	57	67
4	**L**$_1$ (10)	—	1,4-dioxane	42	82
5	**L**$_1$ (10)	—	CH_3CO_2Et	49	82
6	**L**$_1$ (10)	—	toluene	42	75
7[e]	**L**$_1$ (10)	—	DCE	12	75
8	**L**$_2$ (10)	—	DCE	56	5
9	**L**$_3$ (10)	—	DCE	47	35
10	**L**$_4$ (10)	—	DCE	15	11
11	**L**$_5$ (10)	—	DCE	81	5
12	**L**$_6$ (10)	—	DCE	trace	—
13	**L**$_7$ (10)	—	DCE	42	–79
14	**L**$_8$ (10)	—	DCE	36	87
15	**L**$_8$ (10)	LiOH (3.0)	DCE	40	95
16	**L**$_8$ (10)	LiOH (6.0)	DCE	68	98
17	**L**$_8$ (10)	NaOH (6.0)	DCE	59	98
18	**L**$_8$ (10)	^{t}BuOLi (6.0)	DCE	trace	—
19	**L**$_8$ (10)	Cs_2CO_3 (6.0)	DCE	nd[f]	—
20	**L**$_8$' (10)	LiOH (6.0)	DCE	66	–97

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.15 mmol), $Pd(OCOCF_3)_2$ (10 mol%), ligand (10 mol%), base (*y* equiv), solvent (0.3 mL), under air conditions, 10 h. [b] Isolated yield based on substrate **1a**. [c] Determined by chiral HPLC analysis. [d] 30 °C. [e] $Pd(OAc)_2$ (10 mol%). [f] nd = not detected.

Substrate scope of asymmetric palladium catalysis

With the effective catalytic system identified in hand (entry 16, Table 1), we then studied the substrate scope (Figure 2). As shown in Figure 2, phenylboronic acid (**2a**) and *p*-tolylboronic acid (**2b**) were first selected to investigate the influence of substituents (R^1) in the arylalkynyl moiety of yne-allenone **1**. As expected, all these transformations worked smoothly to afford the corresponding cyclobuta[*a*]naphthalen-4(2*H*)-ones **3b**—**3q** in yields of 35%—81% and between 89% and 99% ee except for **3l**. Various substituents including alkyl (methyl **1b** and **1c**, ethyl **1d** and *t*-butyl **1e**), halo (chloro **1f** and **1g**, bromo **1h**), amide (**1i**), sulfonate (**1m**), ester (**1n**) and trifluoromethyl (**1o**) groups located in different positions (*ortho, meta* and *para*) of arylalkynyl motifs were compatible with this reaction. The presence of sterically encumbered substituents in the substrates seems unfavorable for the present reaction, as the conversion of *o*-chlorophenyl analogue **1g** into **3g** only gave a low yield of 35%. Moreover, both 1-naphthyl (1-Np) and 2-thienyl counterparts **1j** and **1k** were proven to be suitable, enabling their cyclization-asymmetrical addition cascades to render the corresponding products **3j** and **3k** in 55% and 50% yields with 96% and 92% ee, respectively. Notably, alkenyl-substituted yne-allenones **1p** and **1q** (*e.g.*, cyclohexenyl **1p** and 2-indenyl **1q**) were applicable for this protocol, furnishing the corresponding enantioenriched cyclobuta[*a*]naphthalen-4(2*H*)-ones **3p** and **3q** in acceptable yields. This asymmetric strategy was also adaptable to the heteroarene-linked yne-allenone because the reaction of **1r** with a thiophene occurred in 55% yield and excellent enantioselectivity (**3r**, 97% ee). The reaction of *tert*-butyl analogue **1l**, however, resulted in severe decomposition, with only observation of a trace amount of product **3l**, demonstrating that the conjugated group stabilized yne-allenones prove to be important. Next, we introduced different functional groups (R^2) including methyl, methoxy, fluoro, and chloro into the C4 or C5 position of the internal arene ring of substrates **1** and expanded their synthetic utility of the present reaction. Satisfyingly, all those substituents (**1s**—**1gg**) did not hamper their corresponding catalytic processes, and the corresponding products **3s**—**3gg** were afforded with yields of 38%—84% and high enantioselectivities. Of these substrates, styryl-substituted yne-allenone **1gg** could also be transformed into product **3gg** with 97% ee, albeit in a low yield of 38%. Alternatively, substrate **1hh**, an estrone analogue, enabled asymmetric palladium-catalysis to give cyclic product **3hh** that comprises both estrone and cyclobuta[*a*]naphthalen-4(2*H*)-one units in 73% yield, 98% ee and >20 : 1 dr.

Among them, chloro functionality at C4 position of internal arene ring (**1v**) would provide flexible late-stage modifications through modern cross coupling reactions, and thus this substrate was selected as a representative electrophile to explore the scope of arylboronic acids (Figure 3). Reactions with structurally various arylboronic acids **2** proceeded well to deliver high yields of the

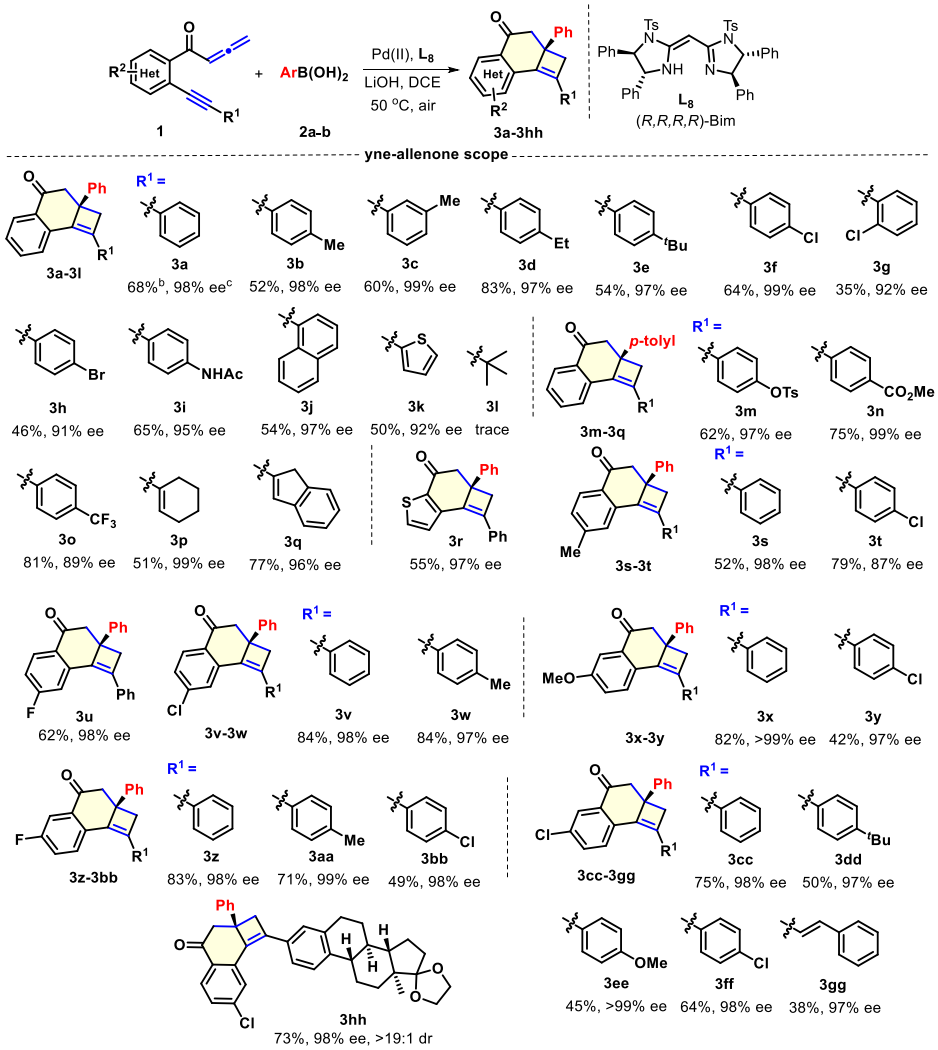


Figure 2 The scope for the synthesis of (*S*)-**3a**—**3hh**. i) Reaction conditions: **1** (0.05 mmol), **2** (0.15 mmol), $Pd(OCOCF_3)_2$ (10 mol%), (*R*,*R*,*R*,*R*)-*N*,*N*'-disulfonyl Bim (10 mol%), LiOH (6.0 equiv), DCE (0.3 mL), under air conditions, 10 h. ii) Isolated yield in brackets based on substrates **1**. iii) ee value in brackets was determined by chiral HPLC analysis.

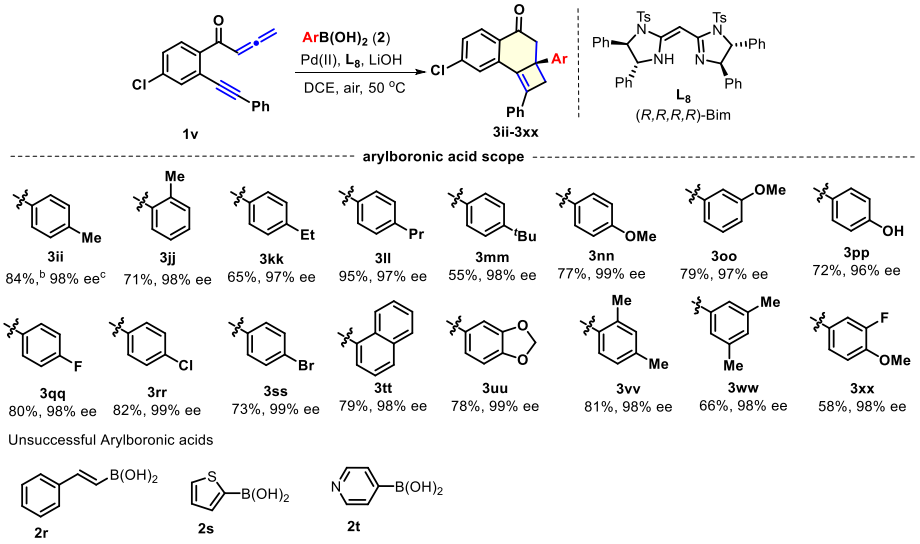


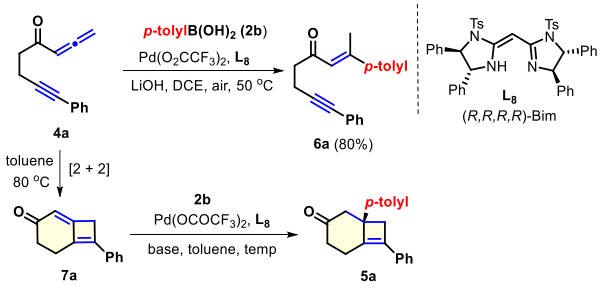
Figure 3 The scope for the synthesis of (*S*)-**3ii**—**3xx**. i) Reaction conditions: **1v** (0.05 mmol), **2** (0.15 mmol), $Pd(OCOCF_3)_2$ (10 mol%), (*R,R,R,R*)-Bim (10 mol%), LiOH (6.0 equiv), DCE (0.3 mL), under air conditions, 10 h. ii) Isolated yield in brackets based on substrate **1v**. iii) ee value in brackets was determined by chiral HPLC analysis.

desired products with excellent asymmetric induction. Both electron-rich (*e.g.*, methyl, **2b** and **2c**; ethyl, **2d**; *n*-propyl, **2e**; *n*-butyl, **2f**; methoxy, **2g** and **2h** and hydroxyl **2i**) and electron-deficient (*e.g.*, fluoride, **2j**; chloride, **2k** and bromide, **2l**) groups were well tolerated, affording cyclobuta[*a*]naphthalen-4(2*H*)-ones **3ii**—**3ss** in 55%—95% yields with excellent ee values (97%—99%). Specifically, these nucleophiles can possess a bicyclic system such as 1-naphthyl (1-Np, **2m**) and 4-piperonyl (**2n**) groups. Alternatively, disubstituted nucleophiles (2,4-dimethylphenyl, **2o**; 3,5-dimethylphenyl, **2p**; 3-fluoro-4-methoxyphenyl, **2q**) were proven to be workable reaction partners, furnishing products in high yield and excellent enantioselectivity (**3vv**—**3xx**, Figure 3). When the aryl fragment in the boronic acid moiety was alternated with a conjugated unsaturated group such as styryl (**2r**) or heteroaryl (2-thienyl, **2s** and 4-pyridinyl, **2t**), regretfully, their corresponding nucleophiles were not compatible for the target reaction under the standard conditions. The absolute configuration of **3rr** was confirmed by X-ray diffraction analysis and its derivatives were assigned by analogy (CCDC 1888083, see Supporting Information).

Expanded study of asymmetric palladium catalysis

To expand the utility of this methodology, we devoted our next efforts to exploring the [2 + 2] cycloaddition-asymmetric 1,4-addition by adopting the preformed alkyl-tethered yne-allenones **4**. The reaction of **4a** with **2b** was carried out under the above reaction conditions, and only adduct product **6a**, which is referred as Michael product and was proposed to be formed by 1,4-addition catalyzed by Pd, and then alkene isomerization (see Supporting Information for discussions), was obtained in 80% yield. To achieve this asymmetric synthesis of 6-4 product **5a**, the [2 + 2] adduct product **7a** was first prepared and then was used to react with **2b** in toluene at 50 °C by employing $Pd(OCOCF_3)_2$/(*R,R,R,R*)-*N,N'*-disulfonyl Bim **L8** complex and LiOH as the base, delivering the expected cyclobutene product **5a** in 45% yield with 68% ee (Table 2, entry 1). Subsequently, a variety of bases, such as LiO^{t}Bu, NaO^{t}Bu, KO^{t}Bu, K_2CO_3, Cs_2CO_3, Li_2CO_3, and $Mg(O^tBu)_2$ were tested for this transformation (entries 2—8). Among these bases, the former five gave unsatisfactory results regarding the yield and enantioselectivity (entries 2—6); in contrast, and to our delight, the latter two bases drove this transformation to work more efficiently, providing higher yields and enantioselectivities of **5a** as compared with LiOH (entries 7 and 8 vs entry 1)—and of these two bases, $Mg(O^tBu)_2$ was the better choice for this catalytic process (entry 8). Reducing the reaction temperature to 40 °C resulted in a higher yield and ee value of **5a** (66% yield, and 93% ee, entry 9).

Table 2 Optimization of the reaction conditions[a]



Entry	Base	Temp/°C	Yield[b]/%	ee[c]/%
1	LiOH	50	45	68
2	LiO^{t}Bu	50	50	30
3	NaO^{t}Bu	50	48	70
4	KO^{t}Bu	50	45	15
5	K_2CO_3	50	52	50
6	Cs_2CO_3	50	40	60
7	Li_2CO_3	50	55	90
8	$Mg(O^tBu)_2$	50	64	90
9	$Mg(O^tBu)_2$	40	66	93

[a] Reaction conditions: **4a** (0.05 mmol), **2b** (0.15 mmol), $Pd(OCOCF_3)_2$ (10 mol%), **L8** (12 mol%), base (2.0 equiv), solvent (0.3 mL), under air conditions, 120 h for second step. [b] Isolated yield based on substrate **4a**. [c] Determined by chiral HPLC analysis.

We then examined the scope and limitation of this asymmetric catalytic reaction through a two-step strategy from alkyl-tethered yne-allenones **4** and arylboronic acids **2** (Figure 4). Alkyl-tethered yne-allenones **4b**—**4d** carrying either electronically neutral (H, **4a**), rich (methyl, **4b** and methoxy **4c**), or poor (chloro **4d** and bromo **4e**) groups attached by the aryl moiety were well accommodated with the reaction of **2b** or **2k**, giving the corresponding enantioenriched cyclobutenes **5b**—**5i**, albeit with moderate to good yields. The investigation on the scope of arylboronic

acids revealed that other substituents such as methyl, methoxy, and bromo at the *para*-position of aromatic rings were compatible with this catalytic system. Moreover, disubstituted arylboronic acids were suitable for this asymmetric 1,4-addition, providing products **5m** and **5n** with moderate yields and high enantioselectivities. From the above observations, alkyl-tethered yne-allenones showed lower reactivity than that of benzene-linked yne-allenones.

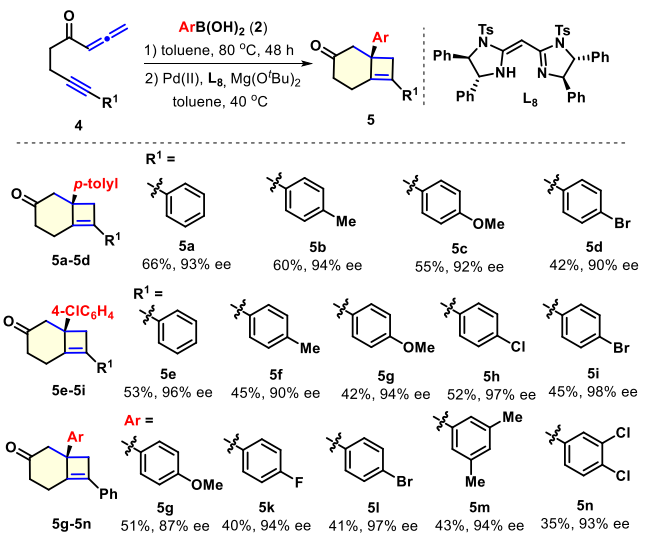


Figure 4 The scope for the synthesis of (*S*)-**5a**—**5n**. i) Reaction conditions: **4** (0.05 mmol), **2** (0.10 mmol), $Pd(OCOCF_3)_2$ (10 mol%), (*R*,*R*,*R*,*R*)-*N*,*N*'-disulfonyl Bim **L**$_8$ (12 mol%), $Mg(O^tBu)_2$ (2.0 equiv), toluene (0.5 mL), under air conditions, 120 h for second step. ii) Isolated yield in brackets based on substrate **4**. iii) ee value in brackets was determined by chiral HPLC analysis.

Synthetic applications of cyclobutenes

The potential synthetic utility of this method for other molecules was then demonstrated. First, a scale-up reaction was carried out under the standard conditions. We were delighted to find that product **3v** was obtained in 85% yield on a 2.0 mmol scale with retaining the excellent enantioselectivity (Figure 5a). Next, the diversifications of the cyclobutene products were conducted (Figure 5b). The reduction of **3v** gave rise to the (2*aS*,4*S*)-cyclobuta[*a*]naphthalen-4-ol **9** in 56% yield and 97% ee (Figure 5b, path i). Moreover, we targeted the synthesis of chiral hydroquinones with quaternary stereocenters with interesting biological properties.[23] Two representative cases of the ozonolysis were performed,[24] which afforded the enantioenriched (*S*)-2,3-dihydronaphthalene-1,4-diones **10a** (Figure 5b, path ii) and **10b** (see Information Supporting) in quantitative yields without loss of ee values. The resulting (*S*)-2,3-dihydronaphthalene-1,4-dione **10a** was subjected to the reaction of hydrazine hydrate in a one-pot two-step process, affording (*R*)-4a,5-dihydrobenzo[*h*]cinnolin-6(2*H*)-one **11** in 95% yield and 97% ee (Figure 5b, path iii). Reaction of **10a** with phenylhydrazine in HOAc gave naphthalene-1,4-dione-derived hydrazone **12** in 65% yield with the retention of ee value (97%, Figure 5b, path iv). Treatment of cyclobutene product **3v** with *p*-tolyl sulfonyl hydrazine resulted in cyclobutene-derived tosylhydrazone **13** in 71% yield and 97% ee (Figure 5b, path v).

DFT study of reaction mechanisms

To gain more insights into the reaction mechanism and its high enantioselectivity, density functional theory (DFT) calculations at the SMD(DCE)/B3LYP/6-311+G(d,p) (SDD for Pd)//B3LYP/6-31+G(d) (LANL2DZ for Pd) level[25] have been performed (see Supporting

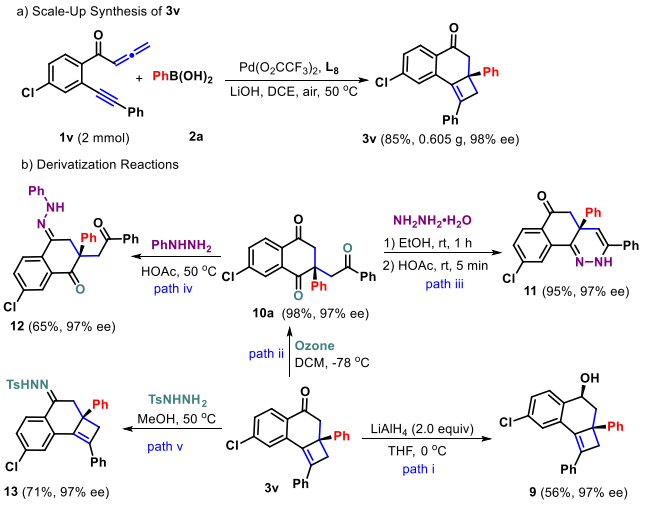


Figure 5 Scale-up synthesis and application of cyclobutene **3v**.

Information for details). We chose substrate **1a**, **2a** and ligand **L**$_8$' to investigate its reaction mechanism. To accelerate calculations, the *para*-toluenesulfonyl group and phenyl group in the original **L**$_8$ were simplified as the smaller methanesulfonyl and methyl groups, respectively. Based on previous works[14a,26-27] and our results, the energy profile was drawn according to the relative Gibbs energies in DCE solution (ΔG_{sol}, Figure 6a). In the presence of **2a**, **L**$_8$', and base (LiOH), the precursor $Pd(TFA)_2$ is firstly transformed to the reactive intermediate **Int1**, a Pd(II)-phenylborate complex. Then, the carbon-boron bond in **Int1** coordinates to the palladium center via **TS1** to give **Int2** with a computed activation free energy of 17.7 kcal/mol (this step is endergonic by 12.7 kcal/mol in ΔG_{sol}). The oxidation addition of this carbon-boron bond to palladium through **TS2** subsequently takes place, affording a phenylpalladium complex **Int3**. This step is an exergonic process (by 22.5 kcal/mol) with an activation free energy of 3.8 kcal/mol. Ligand exchange reaction between **Int3** and the substrate then gives rise to a more stable intermediate **Int4**. Then, from the substrate-ligated intermediate **Int4**, there are two possible pathways. A stepwise intramolecular Pd-catalyzed [2 + 2] cycloaddition of **1a** in **Int4** via **TS3**, **Int5**, and **TS5** with an activation free energy of 19.8 kcal/mol is favored, leading to the formation of **Int7**. The second step in this Pd-catalyzed [2 + 2] reaction is almost barrierless. The present Pd-catalyzed [2 + 2] process is exergonic by 36.5 kcal/mol and is irreversible (the followed reactions after this step are downhill processes). Alternatively, the direct 1,4-addition or Michael addition of phenyl group to **1a** in **Int4** via **Int6** and **TS4** to **6'a** is disfavored than the Pd-catalyzed [2 + 2] process by 1.7 kcal/mol and can be excluded for further consideration. This is the reason why experimentally such a Michael addition product was not formed when one-pot reaction was carried out for **1a**, different from substrate **4a** (see later on discussions).

After the Pd-catalyzed [2 + 2] reaction, intermediate **Int7** that has the carbonyl oxygen coordination is proposed to undergo a ligand exchange process to give **Int8**, which has an alkene moiety in the [2 + 2] cycloadduct as the ligand (this process is endergonic by 13.1 kcal/mol in ΔG_{sol}). This step is required for later on palladium-catalyzed Michael addition of phenyl group to enone in **Int8**. The 1,4-addition or Michael addition via **TS6** gives rise to a $^1\eta$-complex **Int9** with a computed activation free energy of 15.1 kcal/mol. A $^3\eta$-enolate complex **Int10** is easily formed from **Int9**, and a water molecule, which is expected to be present in the reaction system in a trace amount, acts as a ligand and converts **Int10** to **Int11**. Through **TS7**, the intramolecular protonation of **Int11** will afford the product-coordinated complex **Int12** with an

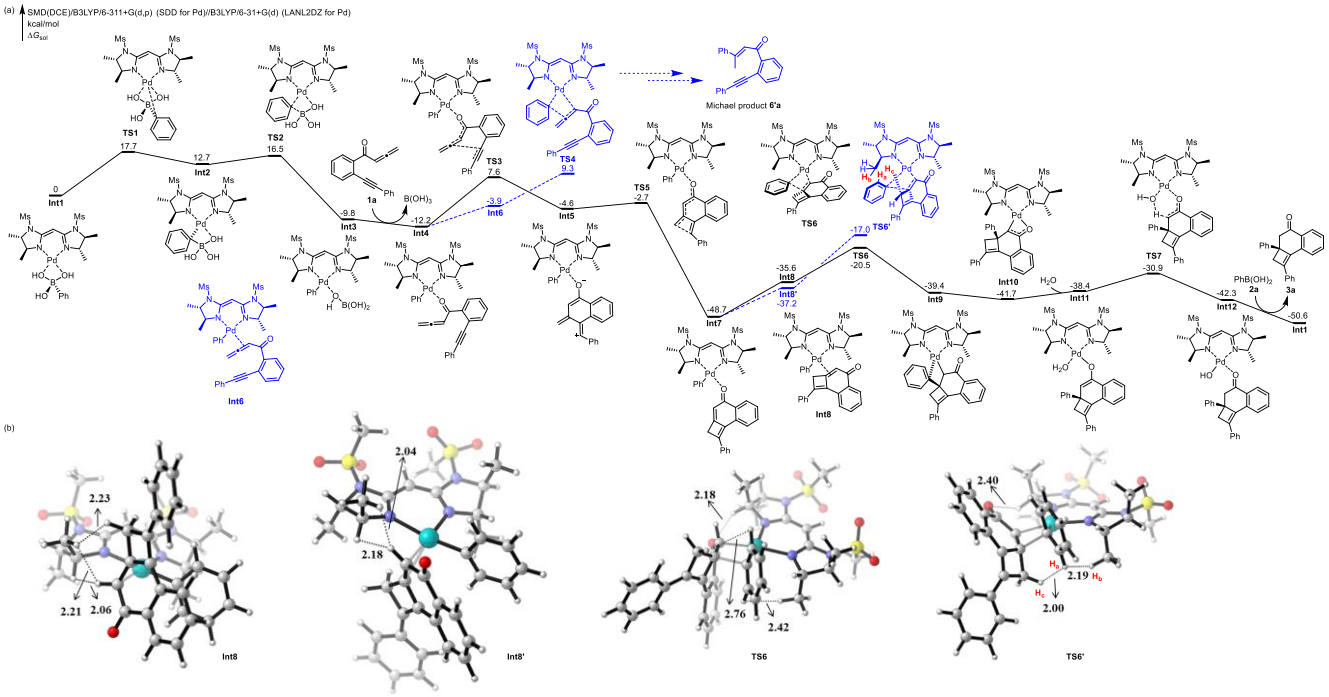


Figure 6 Gibbs free energy profiles of the catalytic process and the key computed structures in the formation of **3a** (bond distances in angstrom).

activation free energy of 7.5 kcal/mol. After a ligand exchange of **Int12** and **2a**, the final product **3a** is liberated and the reactive **Int1** is regenerated. In this catalytic cycle, the irreversible 1,4-addition of Michael addition via **Int8** and **TS6** is the rate-determining step, which has an activation free energy of 28.2 kcal/mol.

As mentioned above, **1a** at room temperature can undergo the intramolecular [2 + 2] reaction to give **8a** gradually (this is referred as metal-free [2 + 2] reaction). Therefore, there is a possibility that some **8a** generated by the metal-free [2 + 2] reaction of **1a** reacts with **2a** under the catalysis of Pd to generate **3a**. DFT calculations indicated that this is disfavored because the metal-free [2 + 2] reaction requires an activation free energy of 23.5 kcal/mol, about 3.7 kcal/mol higher than that of the Pd-catalyzed [2 + 2] reaction as shown in Figure 6 (details can be found in Supporting Information).

Certainly, if **8a** is generated, it cannot go back to **1a** because this needs an activation free energy of 56.5 kcal/mol. Therefore, if using **8a** as the substrate (or **8a** was partially formed in **1a**), it can also undergo Pd-catalyzed addition reaction with **2a** to produce **3a**, as supported by DFT calculations (see Supporting Information).

Origin of enantioselectivity

According to the mechanism mentioned above, the rate- and enantioselectivity-determining step of this reaction is Michael addition of the phenylpalladium complex to the [2 + 2] cycloadduct **8a** (see Supporting Information). Formation of **(*R*)-3a** via **TS6** has an activation free energy of 28.2 kcal/mol. If **Int8** changes the coordination mode with the [2 + 2] cycloadduct, leading to **Int8'**, Michael addition by phenyl group requires an activation free energy of 31.7 kcal/mol, giving rise to **(*S*)-3a**. The free energy difference of **TS6** and **TS6'** is 3.5 kcal/mol, indicating that **(*R*)-3a** will be the major product rather than **(*S*)-3a** when L_8' is used. This is consistent with the experimental result that **(*R*)-3a** was obtained with 97% ee. We attribute this difference to steric repulsions between the phenylpalladium moiety, chiral ligand L_8' and [2 + 2] cycloadduct **8a**, the direct [2 + 2] reaction product of allene and alkyne in **1a**. The real models of **TS6** and **TS6'** were also taken into considerations, and their free energy difference was 4.2 kcal/mol (see Supporting Information), which indicated that our simplification of reaction model does not affect the results.

Let's examine in details the steric interactions in both intermediates **Int8** and **Int8'** and transition states **TS6** and **TS6'**. The three hydrogen-hydrogen (H-H) distances in **Int8** are 2.06, 2.21 and 2.23 Å, while there are only two H-H repulsion in **Int8'** (the H-H distances are 2.04 and 2.18 Å, see Figure 6b), suggesting that **In8** experiences more steric repulsions than **Int8'** does (**Int8** is less stable by 1.6 kcal/mol than **Int8'**). However, in transition states, the Michael addition prefers **TS6** over **TS6'** (28.2 kcal/mol vs. 31.7 kcal/mol from **Int7**). This is because there is strong steric repulsions in **TS6'** (the H_a in phenyl group has repulsions with H_b in L_8' and H_c in **8a**, and their distances are 2.19 and 2.00 Å, respectively, see these in Figures 6a and 6b). Such steric repulsions in **TS6** are not found. Therefore, **3a** is generated with high enantioselectivity.

The above calculations can explain the enantioselectivity without adding LiOH or NaOH (Table 1, entry 14). When LiOH or NaOH was added, the ee of the reaction increased by 10% (Table 1, entries 16—17). We here just hypothesize that different solvation effects on the Michael addition transition states, due to the presence of salts, could be the reason for these phenomena.

Understanding the (competing) metal-free [2 + 2] reactions and formation of 6a

The reaction of **1a** with **2a** can be carried out either in one-pot or by a two-step process through forming metal-free [2 + 2] process to **8a** first, followed by Pd-catalyzed 1,4-addition or Michael addition of **2a** to **8a**. The reason for the one-pot reaction is the competing Pd-catalyzed Michael addition of **2a** to **1a** vis **TS4** to **6'a** is disfavored, as discussed above (Figure 6). Now let's discuss why for substrate **4a**, a two-step process is needed. For substrate **4a**, in the presence of Pd catalyst, the formation of **5a** (the 6-4 product with bridgehead Ph group), with an overall activation free energy of 25.1 kcal/mol, is disfavored than the Pd-catalyzed 1,4-addition or Michael addition of **2a** to **4a** for the formation of Michael product **6a**, which requires an activation free energy of 21.4 kcal/mol (see Supporting Information). To avoid formation of the Michael product **6a**, the reaction of **4a** had

to be carried out separately.

The different reaction selectivity of **1a** and **4a** toward **2a** is attributed to the linkers of yne-allenones. **1a** has an aromatic linker and this helps **TS3** forming tricyclic enones with a larger conjugated system (Figure 6), whereas this is absent in **TS13** in the Pd-catalyzed [2 + 2] cycloaddition transition state for the formation of possible [2 + 2] cycloadduct for substrate **4a** (see this and more other discussions in Supporting Information). The second reason is that **1a** in its ground state with its alkyne and diene moieties in the *cis* configuration adopts a reactive conformation and is easier for the desired Pd-catalyzed [2 + 2] reaction, compared to the Michael addition to the formation of **6'a**. But **4a** in its ground state with the two reactive groups in a *trans* configuration is not in the reactive conformation, which consequently disfavors the desired Pd-catalyzed [2 + 2] reaction compared to the Michael addition to the formation of **6a**.

In addition, we have computed the metal-free [2 + 2] cycloaddition of **4a**, which has an activation free energy of 29.8 kcal and is exergonic by 27.2 kcal/mol (see Supporting Information). Therefore, raising reaction temperature to 80 °C is critical for this [2 + 2] process.

Conclusions

In conclusion, we have achieved the first asymmetric synthesis of 6-6-4 and 6-4 cyclic molecules with ring-junction all-carbon stereocenters by Pd(II)/chiral Bim-catalyzed asymmetric reaction of yne-allenones and arylboronic acids. This reaction has broad scope and high enantioselectivities and can be carried out in air. Realization of 6-6-4 skeleton here is a one-step process while synthesizing 6-4 skeleton is a two-step process, which begins with intramolecular [2 + 2] reaction of allenes with alkynes, followed by Pd-catalyzed asymmetric addition of arylboronic acids to cyclic enones generated in the first step. This is also the first report using easily prepared chiral (*R*,*R*,*R*,*R*)-Bim $\mathbf{L_8}$ ligand for the Pd-catalyzed 1,4-addition of aryl boronic acids to enones. DFT calculations have been applied to reveal how the present reactions take place and answer why **1a**'s reaction is a one-step process while **4a**'s reaction must be a two-step process. Enantioselectivity and competition of side reactions have also been investigated. Further application of this catalysis is currently underway and will be reported in due course.

Experimental

General procedure for the synthesis of products 3 and 5

In a screw-cap sealed reaction tube, 1-(2-(phenylethynyl)phenyl)buta-2,3-dien-1-one (**1a**, 0.05 mmol, 12.2 mg), phenylboric acid (**2a**, 0.15 mmol, 3.0 equiv, 18.3 mg), $Pd(OCOCF_3)_2$ (0.005 mmol, 10 mol%, 1.7 mg), Bim ligand $\mathbf{L_8}$ (0.005 mmol, 10 mol%, 3.8 mg), LiOH (6.0 equiv, 7.2 mg) were mixed in DCE (0.3 mL). Then the tube was stirred at 50 °C under air conditions for 10 h until complete consumption of starting material as monitored by TLC (petroleum ether : ethyl acetate 5 : 1) analysis. After the reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure, and the crude product was purified through preparative thin layer chromatography to obtain chiral desired product **3a**.

A solution of **4a** (1.0 mmol, 196.0 mg) and toluene (10 mL) was stirred at 80 °C for 48 h until TLC indicated complete consumption of the starting material, and then the mixture was cooled to room temperature. The residue was purified by chromatography on silica gel with petroleum ether/ethyl acetate (petroleum ether : ethyl acetate = 15 : 1) as the eluent to afford 7-phenylbicyclo[4.2.0]octa-1,6-dien-3-one **7a** (117.6 mg, 60% yield). In a screw-cap sealed reaction tube, **7a** (0.05 mmol, 9.8 mg), *p*-tolylboronic acid **2b** (0.10 mmol, 2.0 equiv, 13.6 mg), $Pd(OCOCF_3)_2$ (0.005 mmol, 10 mol%, 1.7 mg), $\mathbf{L_8}$ (0.006 mmol, 12 mol%, 4.6 mg), $Mg(O^tBu)_2$ (0.1 mmol, 2.0 equiv, 17.0 mg) were mixed in toluene (0.5 mL). Then the vial was stirred at 40 °C under air conditions for 120 h until complete consumption of starting material as monitored by TLC (petroleum ether : ethyl acetate 5 : 1) analysis. After the reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure, and the crude products were purified by silica gel column chromatography (petroleum ether : ethyl acetate = 20 : 1) to get chiral desired product **5a**.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.202200211.

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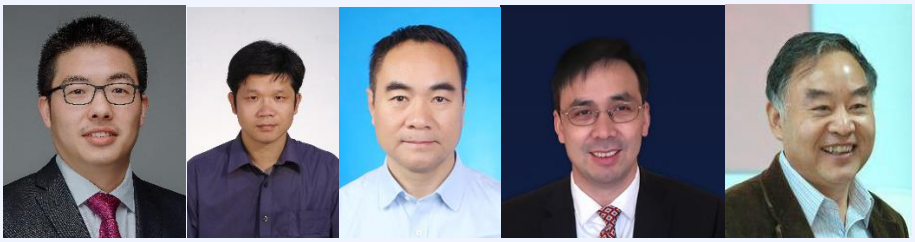

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