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Pd-Catalyzed Enantioselective Syntheses of Trisubstituted Allenes via Coupling of Propargylic Benzoates with Organoboronic Acids

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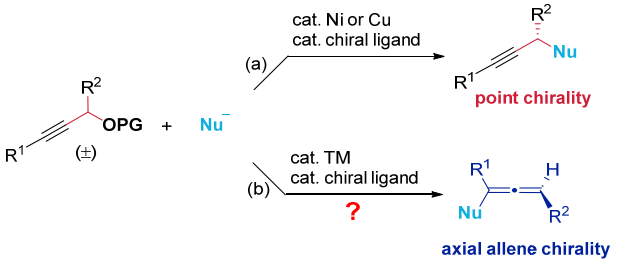
ABSTRACT: Enabled by the newly developed ligand, Ming-Phos, the first example of palladium-catalyzed highly enantioselective coupling of racemic propargylic benzoates with organoboronic acids for chiral allenes synthesis has been developed. Excellent asymmetric induction has been achieved with a decent substrate scope. Synthetic potentials for the construction of polycyclic compounds with multiple chiral centers have been demonstrated.

INTRODUCTION

As an important class of unsaturated hydrocarbons, allenes are different from alkenes, 1,3-alkadienes, and alkynes due to the intrinsic axial chirality of the 1,2-diene functionality[1,2] and have been drawing more and more attention from organic chemists,[3] medicinal chemists,[4] and materials scientists.[5] On the other hand, transition metal-catalyzed cross coupling reaction of propargylic alcohol derivatives and organometallic reagents has also been applied to the syntheses of racemic allene.[6] So far, chiral allene syntheses via the chirality transfer strategy utilizing optically pure propargylic alcohols derivatives and organometallic reagents as the starting materials have been relatively well developed.[7-12] On the other hand, enantioselective coupling of propargylic alcohol derivatives with hard nucleophiles to afford chiral alkynes has been reported (Scheme 1, path a).[13] Such a catalytic enantioselective coupling for chiral allenes syntheses has never been realized (Scheme 1, path b).[14,15] Recently, one of the corresponding authors, Junlinag Zhang, developed a new type of chiral sulfinamide-phosphine ligands, which have demonstrated very unique potentials in enantioselective catalysis.[16] With the joint efforts of these two groups,[17n] herein, we are able to conquer this challenge and report here the first palladium-catalyzed enantioselective coupling reaction of readily available racemic propargylic alcohol derivatives with organoboronic acids by using Ming-Phos affording allenes with an excellent enantioselectivity.[17]

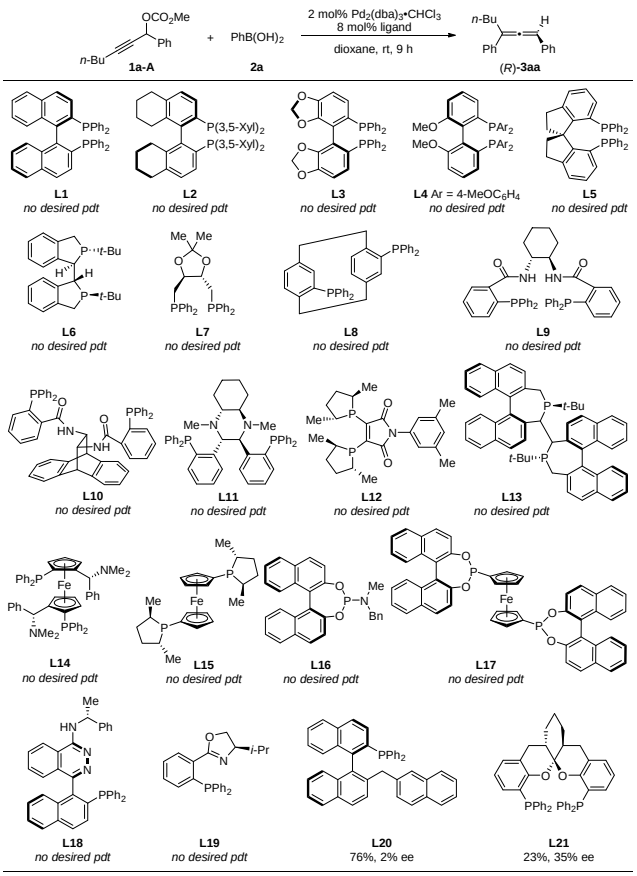
Scheme 1. Transition Metal-Catalyzed Coupling Reaction from Racemic Propargylic Alcohol Derivatives.



RESULTS AND DISCUSSION

We began our study on the coupling of 1-phenylhept-2-ynyl methyl carbonate (**1a-A**) and phenylboronic acid (**2a**). Various commercially available chiral ligands were tested for this reaction in dioxane under the catalysis of $Pd_2(dba)_3$•$CHCl_3$ at the room temperature (Table 1). Unfortunately, no allene product was detected with **L1**-**L19**. The reaction proceeded smoothly to afford (*R*)-**3aa** in 76% NMR yield with **L20** as the ligand; however, the enantiomeric excess was only 2%. SKP ligand **L21** could improve the ee to 35%.

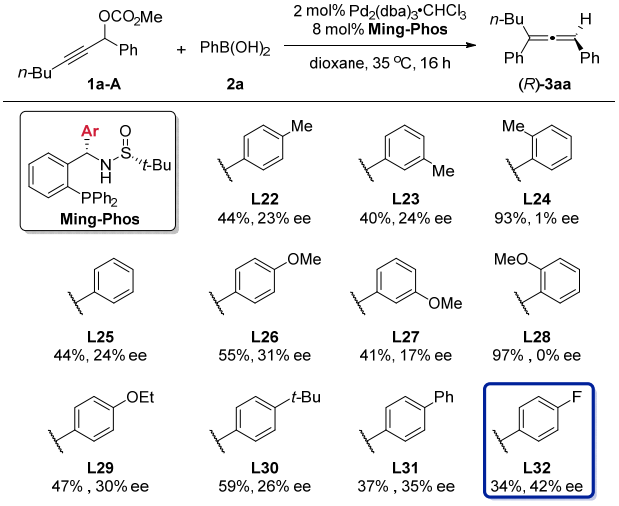
Table 1. Primary Ligand Screening with 1a-A as Substrate.[a]



[a] The reaction was conducted with **1a-A** (0.5 mmol), **2a** (0.75 mmol), $Pd_2(dba)_3$•$CHCl_3$ (2.0 mol%), and ligand (8 mol%) in dioxane (2 mL) at r.t. under Ar atmosphere. Tthe yield was determined by ^1H NMR analysis and ee value was determined by HPLC analysis.

To our delight, Ming-Phos **L22** could serve as the ligand to yield 44% of (*R*)-**3aa** with 23% ee (Table 2). Benefitted from the easy synthesis of Ming-Phos, we designed a series

Table 2. The First Round Screening of Ming-Phos Ligands with 1a-A as Substrate.[a]

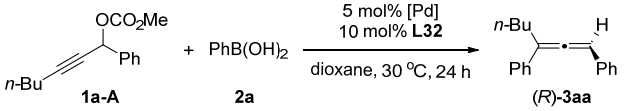


[a] The reaction was conducted with **1a-A** (1.0 mmol), **2a** (1.2 mmol), $Pd_2(dba)_3$•$CHCl_3$ (2.0 mol%), and ligand (8 mol%) in dioxane (2 mL) at 30 °C under Ar atmosphere. The yield was determined by ^1H NMR analysis and ee value was determined by HPLC analysis.

of Ming-Phos with different substituents and examined their performances in this asymmetric coupling reaction (Table 2). The efficiency of *para*- or *meta*-methyl substituted Ming-Phos (**L22** and **L23**) was similar. The *ortho*-methyl substituted **L24** could afford 93% of allene product (*R*)-**3aa**, however, the ee was only 1%. *para*-Methoxy-substituted Ming-Phos **L26** could improve the ee to 31%. The performance of *ortho*-methoxy-substituted **L28** was similar to **L24**. It's obvious that *para*-substituent is more efficient for this asymmetric transformation. Other *para*-substituents, such as OEt, *t*-Bu, Ph, and F were then studied, Ming-Phos **L32** could afford 34% of (*R*)-**3aa** with 42% ee.

Various palladium catalysts were then screened with **L32** as the ligand: No expected allene product was formed with $PdCl_2$, $[Pd(\pi\text{-allyl})Cl]_2$, and $[Pd(\pi\text{-cinnamyl})Cl]_2$ (Table 3, entries 1-3); Lower yields were obtained with $Pd(OAc)_2$, $Pd(acac)_2$, or $Pd(OTf)_2$ (Table 3, entries 4-6); among Pd(0) catalysts, such as $Pd(dba)_2$, $Pd(dmdba)_2$, and $Pd_2(dba)_3$•$CHCl_3$, $Pd(dmdba)_2$ was the best affording 26% of (*R*)-**3aa** with 46% ee (Table 3, entry 8). With the optimal palladium catalyst in hand, we studied the solvent effect (Table 4). Most of the examined ether solvents could afford (*R*)-**3aa** in 22-68% yields with 28-54% ee (entries 1-7). No improvement was obtained when ethyl acetate or chlorine-containing solvents, such as DCM and DCE, was applied (entries 8-10). Moderate yield and enantioselectivity were obtained when toluene was used (entry 11); *c*-hexane was the best in terms of the enantioselectivity (entry 12). With this information, we went back to tune the structure of Ming-Phos again (Table 5) with the *para*-position being substituted with Me (**L22**), OMe (**L26**), *t*-Bu (**L30**), Ph (**L31**), and F (**L32**). **L26** was identified to be the best. Ligands **L33** and **L34** with 1- or 2-naphthyl as the Ar group failed to give better results.

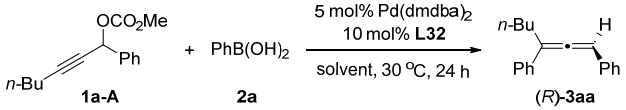
Table 3. The Effect of Palladium Catalysts.[a]



Entry	[Pd]	NMR yield of (*R*)-**3aa** (%)	ee of (*R*)-**3aa** (%)
1	$PdCl_2$	/	/
2	$[Pd(\pi\text{-allyl})Cl]_2$	/	/
3	$[Pd(\pi\text{-cinnamyl})Cl]_2$	/	/
4	$Pd(OAc)_2$	35	26
5	$Pd(acac)_2$	33	19
6	$Pd(OTf)_2$	17	14
7	$Pd(dba)_2$	50	26
8	**$Pd(dmdba)_2$**	**26**	**46**
9	$Pd_2(dba)_3$•$CHCl_3$	61	26

[a] The reaction was conducted with **1a-A** (0.5 mmol), **2a** (1.0 mmol), palladium source ([Pd] 5 mol%), and **L32** (10 mol%) in dioxane (2.0 mL) at 30 °C under Ar atmosphere. The yield was determined by ^1H NMR analysis and ee value was determined by HPLC analysis.

Table 4. The Effect of Solvent.[a]

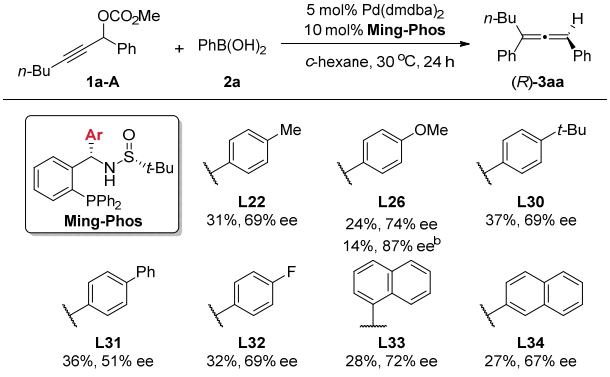


Entry	solvent	NMR yield of (*R*)-**3aa** (%)	ee of (*R*)-**3aa** (%)
1	Et_2O	22	46
2	DME	30	33
3	THF	68	28
4	2-MeTHF	40	35
5	CPME	26	54
6	MTBE	62	38
7	dioxane	26	46
8	EtOAc	50	36
9	DCM	22	29
10	DCE	28	28
11	toluene	48	48
12	***c*-hexane**	**29**	**67**

[a] The reaction was conducted with **1a-A** (0.5 mmol), **2a** (1.0 mmol), $Pd(dmdba)_2$ (5 mol%), and **L32** (10 mol%) in solvent (2.0 mL) at 30 °C under Ar atmosphere. The yield was determined by ^1H NMR analysis and ee value was determined by HPLC analysis.

Reducing the loading of **2a** to 1.2 equiv led to the drop of yield and a higher ee of 87% at a concentration of 0.067 M (Table 5, footnote b). Interestingly, after trial and error, we found that with a mixed solvent of *c*-hexane and MTBE (4:1) the reaction afforded (*R*)-**3aa** in 24% yield with 76% ee in the presence of 0.5 equiv of water (see Table S1 in supporting information for more details). The yield could further improve to 44% when 2.5 mol% of $Pd_2(dba)_3$ was used instead of $Pd(dmdba)_2$.

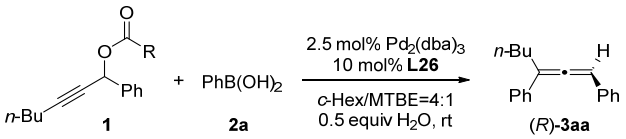
Table 5. The Second Round Screening of Ming-Phos Ligands with $Pd(dmdba)_2$.[a]



[a] The reaction was conducted with **1a-A** (0.5 mmol), **2a** (1.0 mmol), $Pd(dmdba)_2$ (5.0 mol%), and Ming-Phos (10 mol%) in *c*-hexane (1 mL) at 30 °C under Ar atmosphere. The yield was determined by ^1H NMR analysis and ee value was determined by HPLC analysis. [b] The reaction was conducted with 1.2 equiv of **2a** at a concentration of 0.067 M.

Then we turned our attention to the effect of leaving group (Table 6). When benzyl carbonate was used instead of methyl carbonate, the yield of (*R*)-**3aa** was similar but the ee dropped to 63% (Entry 2). We were pleased to found that the enantiomeric excess was further improved to 80% with benzoate as the leaving group (Entry 3). 1-Naphthoate could further increase the ee to 82%, unfortunately the yield dropped to 18% (Entry 4). Other propargylic carboxylates failed to improve the enantioselectivity (Entries 5 and 6). The yield was improved to 96% when 5 mol% of $Pd_2(dba)_3$•$CHCl_3$ and 10 mol% of **L26** were applied (entry 7).

Table 6. The Effect of Leaving Group.[a]

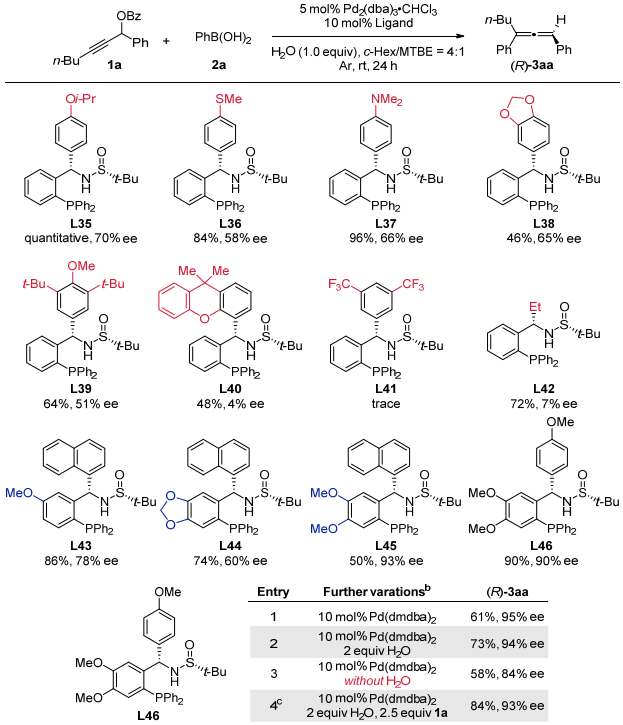


Entry	R	NMR yield of (*R*)-**3aa** (%)	ee of (*R*)-**3aa** (%)
1	OMe	44	74
2	OBn	47	63
3	Ph	24	80
4	1-naphthyl	18	82
5	2-thienyl	33	71
6	Ad	7	77
***7*[b]**	***Ph***	***96***	***73***

[a] The reaction was conducted with **1** (0.1 mmol), **2a** (0.12 mmol), $Pd_2(dba)_3$ (2.5 mol%), **L26** (10 mol%), and H_2O (0.05 mmol) in *c*-Hex/MTBE (1.2 mL/0.3 mL) at rt under N_2 atmosphere. The yield was determined by ^1H NMR analysis and ee value was determined by HPLC analysis. [b] **1** (0.1 mmol), **2a** (0.05 mmol), and $Pd_2(dba)_3$•$CHCl_3$ (5.0 mol%) were used.

Based on these data, the structure of Ming-Phos was tuned for the third time (Table 7). *p*-O*i*-Pr (**L35**), SMe (**L36**), and NMe_2 (**L37**) did not improve the enantioselectivity. Poly-substituted ligands **L38**-**L40** also failed. We also tried the ligand with electron-withdrawing CF_3 substituent (**L41**), but no desired allene product was obtained. The ligand with an ethyl group **L42** was also examined, however, only 7% ee of (*R*)-**3aa** was obtained. With 1-naphthyl substituent the substituent effect of the aryl ring linked to phosphorous atom was studied (**L43** to **L45**) and 4,5-dimethoxyl substituted Ming-Phos **L45** was found to be the best with an ee of 93%. Further changing the 1-naphthyl to 4-methoxy phenyl (**L46**) led the reaction to afford (*R*)-**3aa** with 90% NMR yield and 90% ee. When $Pd_2(dba)_3$•$CHCl_3$ was replaced with $Pd(dmdba)_2$, (*R*)-**3aa** was formed in 61% yield with 95% ee (entry 1). The yield was improved to 73% by increasing the water to 2 equivalents (entry 2). As a control experiment (*R*)-**3aa** was only obtained in 58% yield with 84% ee in the absence of water (entry 3), which demonstrated the importance of water. Further increasing **1a** to 2.5 equivalents led to the optimal reaction conditions: 10 mol% of $Pd(dmdba)_2$, 12 mol% of **L46**, 2.5 equiv of **1a**, and 2.0 equivalent of water in *c*-Hex/MTBE at room temperature affording the desired allene (*R*)-**3aa** in 84% NMR yield with 93% ee.

Table 7. The Third Round Screening of Ming-Phos Ligands with 1a as Substrate.

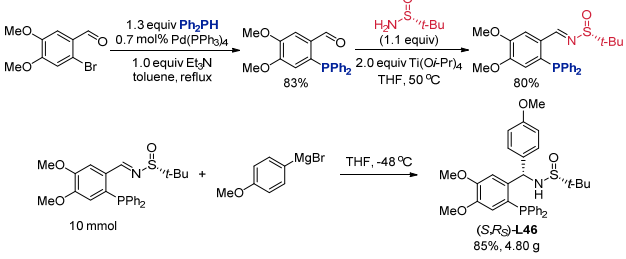


Entry	Further variations[b]	(*R*)-3aa
1	10 mol% Pd(dmdba)$_2$	61%, 95% ee
2	10 mol% Pd(dmdba)$_2$ 2 equiv H_2O	73%, 94% ee
3	10 mol% Pd(dmdba)$_2$ *without* H_2O	58%, 84% ee
4[c]	10 mol% Pd(dmdba)$_2$ 2 equiv H_2O, 2.5 equiv **1a**	84%, 93% ee

[a] The reaction was conducted with **1a** (0.1 mmol) and **2a** (0.05 mmol), $Pd_2(dba)_3$•$CHCl_3$ (5 mol%), ligand (10 mol%), and H_2O (0.05 mmol) in *c*-Hex/MTBE (1.2 mL/0.3 mL) at r.t. under N2 atmosphere. The yield was determined by 1H NMR analysis and ee value was determined by HPLC analysis. [b] Pd(dmdba)$_2$ (10 mol%) and **L46** (12 mol%) were used. [c] The reaction was conducted with **1a** (1.25 mmol) and **2a** (0.5 mmol).

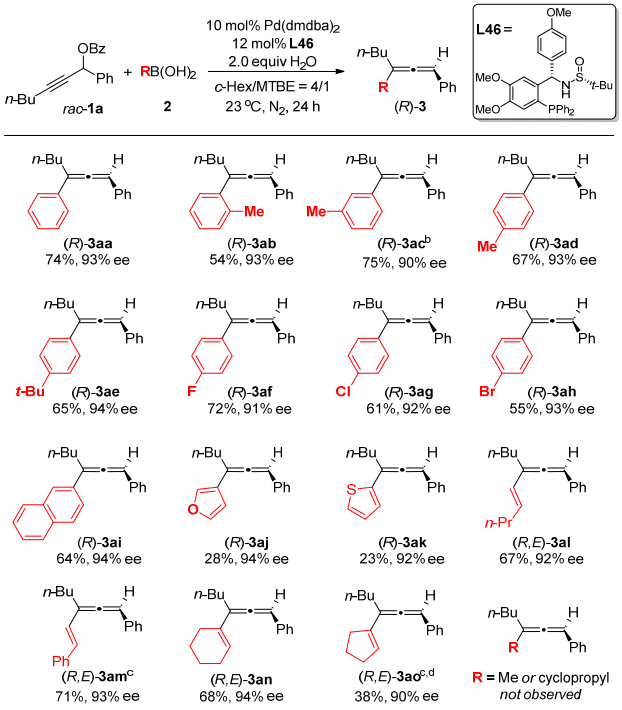
Ming-Phos (S,R_S)-**L46** was easily synthesized on a gram scale from commercial available 2-bromo-4,5-dimethoxybenzaldehyde in three steps (Scheme 2). Pd-catalyzed coupling with diphenylphosphine followed by condensation with (*R*)-*tert*-butansulfinamide would form the (*R*)-sulfinyl imine. Subsequent addition reaction of (4-methoxyphenyl)magnesium bromide to 10 mmol of the (*R*)-sulfinyl imine afforded 4.80 g of (S,R_S)-**L46** in 85% yield.

Scheme 2. Synthesis of (S,R_s)-L46.



With the optimal conditions in hand, we next investigated the generality of the reaction substrates. First, the reactivity of the different boronic acids was tested for the reaction with **1a** (Scheme 3). A variety of organoboronic acids with electron-neutral, electron-rich, and electron-deficient aryl moieties all reacted smoothly with **1a** to form the corresponding trisubstituted chiral allenes. There is no obvious influence on the steric effect since aryl boronic acids bearing the methyl group at the *ortho*-, *meta*-, and *para*-position of the aryl group all afforded the desired products with high ee ((*R*)-**3ab** to (*R*)-**3ad**). Aryl boronic acids substituted with different halides are suitable substrates for this transformation ((*R*)-**3af** to (*R*)-**3ah**). 2-Naphthyl and heteroaryl boronic acids were also applicable, affording products (*R*)-**3ai** to (*R*)-**3ak** with high enantioselectivies. Moreover, alkenyl boronic acids also worked well in this reaction, affording the desired enallene products (*R,E*)-**3al** in 67% yield with 92% ee and (*R,E*)-**3am** in 71% yield with 93% ee. The reaction is amenable to the cyclic alkenyl boronic acids by furnishing the corresponding products with excellent enantioselectivies ((*R,E*)-**3an** and (*R,E*)-**3ao**). However, no desired allene product was observed when alkyl (R = Me or cyclopropyl) boronic acid was applied.

Scheme 3. Scope of Boronic Acids.[a]

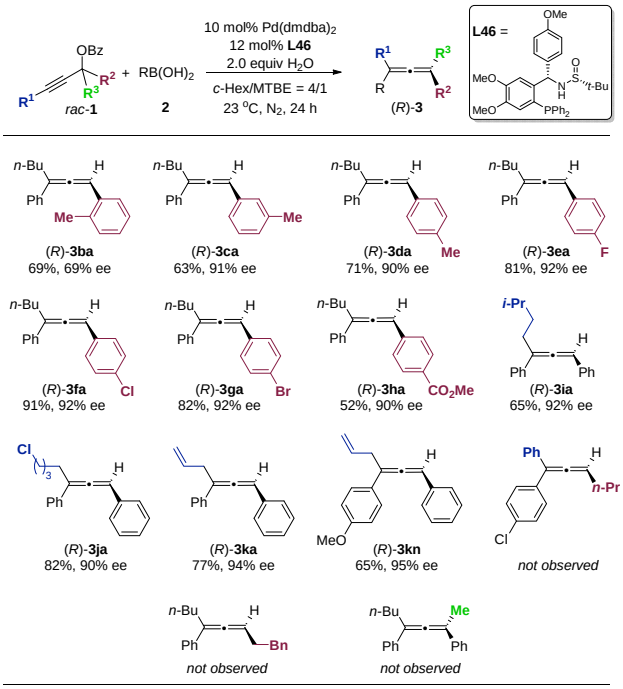


[a] The reaction was conducted with 1.25 mmol of **1a**, 0.5 mmol of **2**, 10 mol% of Pd(dmdba)$_2$, 12 mol% of **L46**, and 1.0 mmol of H_2O in 12 mL of cyclohexane and 3 mL of methyl tertiary-butyl ether at 23 °C for 24 h under N_2 atmosphere. [b] The reaction was carried out at 30 °C for 18 h. [c] The NMR yield is presented with CH_2Br_2 as internal standard. The compound is unstable and characterized by converting to the corresponding cyclic products shown in Scheme 7. [d] 30 h.

Next, we studied the substrate scope of propargylic alcohol derivatives (Scheme 4). *Ortho*-methyl substituted (*R*)-**3ba** was obtained with 69% ee while *meta*- or *para*-methyl substituted (*R*)-**3ca** and (*R*)-**3da** in 90~91% ee, indicating that the steric hindrance has a great effect on the enantioselectivity. Various functional groups, including halogens ((*R*)-**3ea** to (*R*)-**3ga**) and ester ((*R*)-**3ha**) are compatible. R^1 group could be carbon chain substituted with functional groups, such as halogen ((*R*)-**3ja**) and C=C bond ((*R*)-**3ka** and (*R*)-**3kn**). The absolute configuration of the products was established via the specific optical

rotation of (*R*)-**3kn**.[7e] For the substrates with R^2 being an alkyl group were also studied, however, no corresponding allene products were obtained ((*R*)-**3lg** and (*R*)-**3ma**). We tried to synthesize tetra-substituted allenes via the developed protocol by subjecting the racemic tertiary propargylic benzoate (**1l**) and phenylboronic acid (**2a**) to the optimal conditions, however, no desired product was observed. It is noteworthy that excellent regioselectivity was achieved in all these succeeded cases without observing the formation of any alkyne product.[18]

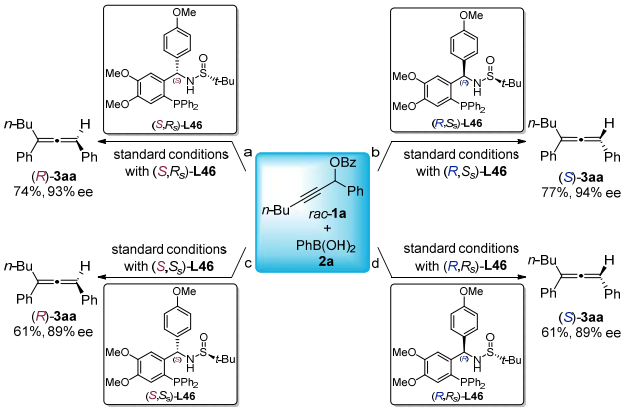
Scheme 4. Scope of Propargylic Derivatives.[a]



[a] The reaction was conducted with 1.25 mmol of **1a**, 0.5 mmol of **2**, 10 mol% of $Pd(dmdba)_2$, 12 mol% of **L46**, and 1.0 mmol of H_2O in 12 mL of cyclohexane and 3 mL of methyl tertiary-butyl ether at 23 °C for 24 h under N_2 atmosphere.

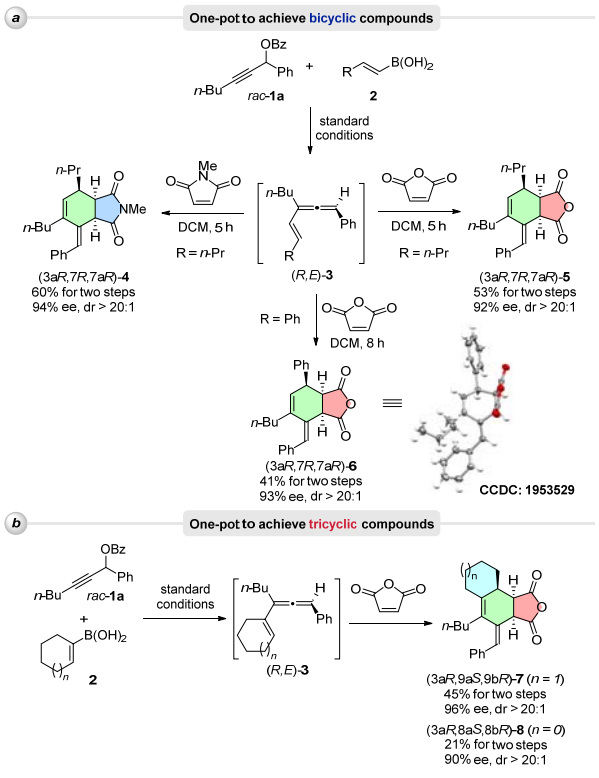
In order to unveil of the role of each chiral center in Ming-Phos for enantiocontrol, the remaining three isomers of (S,R_S)-**L46** were synthesized. As expected, when the enantiomeric ligands (S, R_S)-**L46** and (R, S_S)-**L46** were applied, both enantiomers (*R*)-**3aa** and (*S*)-**3aa** could obtained with 93% and 94% ee, respectively (Scheme 5a & b). (*R*)-**3aa** and (*S*)-**3aa** were afforded with a lower ee of 89% ee when the diastereomeric ligands (S, S_S)-**L46** and (R, R_S)-**L46** were used (Scheme 5c & d). These data led to the conclusion that the configurations of these two chiral centers also helped to ensure the observed excellent enantioselectivity.

Scheme 5. Ligand Effect on Enantioselectivity of the Product.



The synthetic potentials of the alkenyl allenes (*R*,*E*)-**3al** and **3ao** have been demonstrated via their Diels-Alder reaction with *N*-methylmaleimide and maleic anhydride to afford bicyclic products **4**, **5**, and **6** with three continuous chiral centers with excellent enantioselectivities and diastereoselectivities (Scheme 6).[7e] The absolute configurations in these bicyclic products were established by X-ray single crystal diffraction study. Moreover, the one-pot strategy could also be applied for the synthesis of tricyclic compounds **7** and **8** from the cyclic alkenyl boronic acid with an excellent diastereoselectivity.

Scheme 6. Diels-Alder Reaction of En-Allene (*R*,*E*)-3al to (*R*, *E*)-3ao with Dienophiles.

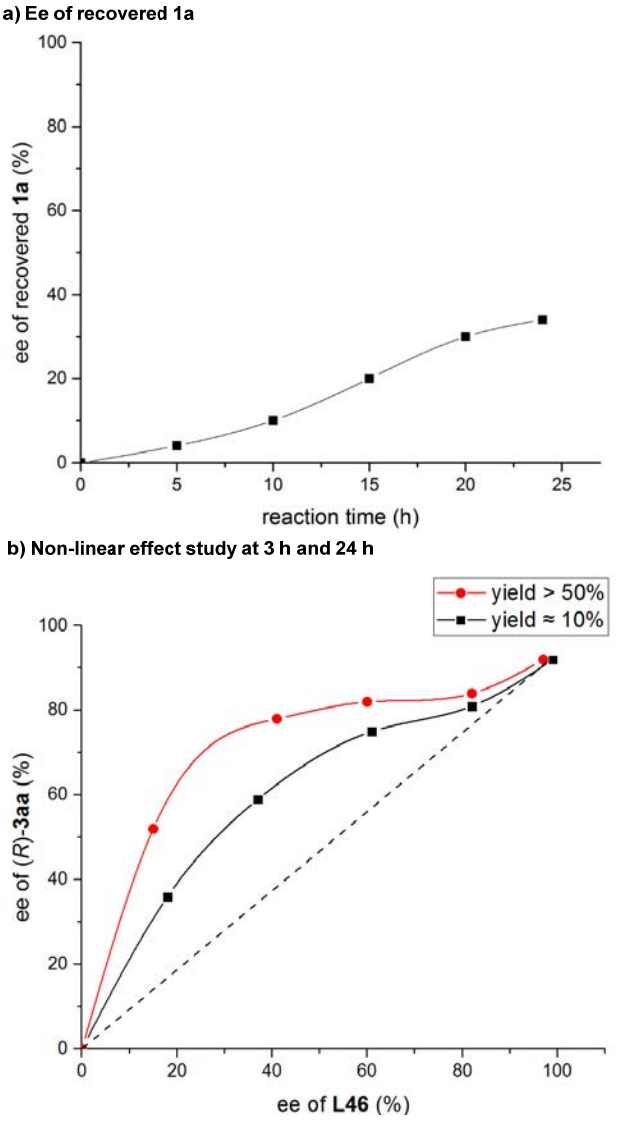


MECHANISTIC STUDIES AND DISCUSSION

In addition, we found the ee of recovered benzoate **1a** after the complete reaction was 35%, indicating that the reaction was mostly a dynamic kinetic resolution (Scheme

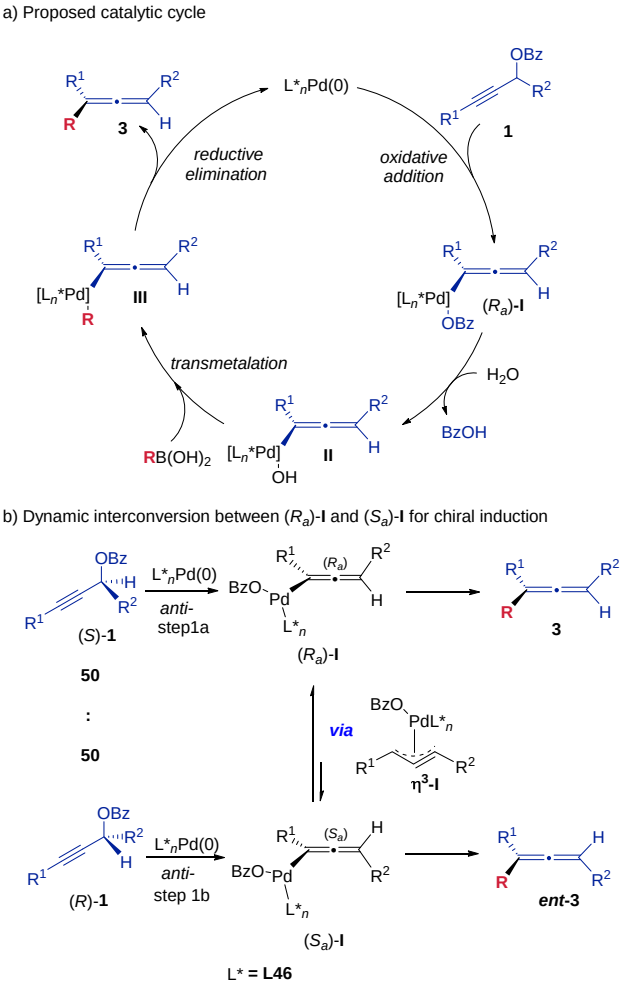
7a). To gain insight into the mechanism, the relationship between the ee value of **L46** and that of **3aa** was investigated (Scheme 7b). A positive non-linear effect was observed at both lower[19] and higher conversions, which indicates that more than one Ming-Phos **L46** may coordinate to the palladium atom.[20-22] However, further studies are needed to clarify the nature of the key intermediates.

Scheme 7. Mechanistic Studies.



Based on these data and literature, a mechanism is proposed as shown in Scheme 8a. L*$_n$Pd(0) (L* = **L46**) would undergo S_N2'-type *anti*-oxidative addition[7] with (*S*)- or (*R*)-enantiomer in the racemic propargylic benzoate **1** to give the same allenylic palladium intermediate (R_a)-**I** through σ-π-σ rearrangement[23] of (S_a)-**I** via the intermediacy of η^3-**I** as shown in Scheme 8b. Due to the ee value of the recovered **1a**, there should be a rate difference for step 1a and step 1b. The benzoate anion may be protonated with water to generate Pd hydroxide intermediate **II**,[7e,7f] which may undergo easier transmetalation with boronic acid to form the intermediate **III**. Reductive elimination of allenylic intermediate **III** affords the allene product **3** and regenerates the catalytically active Pd(0) complex. The flexible coordination nature of the ligand **L46** invited more than just one ligand in the catalytic cycle, which led to the observation of positive non-linear effect shown in Scheme 7b.

Scheme 8. The Proposed Mechanism



CONCLUSION

In summary, we have developed the first asymmetric coupling between propargylic derivatives and organoboronic acids for the synthesis of chiral allenes. It is a new addition to the family of catalytic asymmetric syntheses of allenes without using stoichiometric amounts of chiral starting materials: Enabled by the newly developed Ming-Phos, this Pd-catalyzed reaction proceeds efficiently under mild conditions with a decent compatibility of synthetically usefully functional groups. Preliminary mechanistic studies demonstrated that the reaction was mostly dynamic kinetic resolution. Further studies in this area including the exact role of water on the reaction are being actively pursued in this laboratory.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization and NMR spectra for obtained compounds (PDF)

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Notes

The authors declare no competing financial interests.

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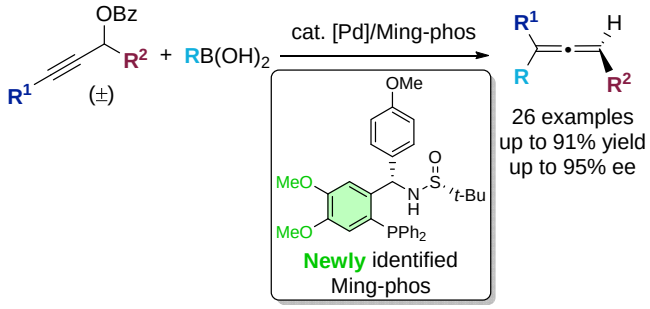
OBz
R2
R1
(±)
+ RB(OH)2
cat. [Pd]/Ming-phos
OMe
MeO
MeO
O
S
N
H
t-Bu
PPh2
Newly identified
Ming-phos
R1
H
R
R2
26 examples
up to 91% yield
up to 95% ee