Asymmetric Catalysis

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Copper-Catalyzed Enantioselective Allyl–Allyl Coupling between Allylic Boronates and Phosphates with a Phenol/N-Heterocyclic Carbene Chiral Ligand

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Abstract: *Copper-catalyzed enantioselective allyl–allyl coupling between allylboronates and either Z-acyclic or cyclic allylic phosphates using a new chiral N-heterocyclic carbene ligand, bearing a phenolic hydroxy, is reported. This reaction occurs with exceptional S_N2'-type regioselectivities and high enantioselectivities to deliver chiral 1,5-diene derivatives with a tertiary stereogenic center at the allylic/homoallylic position.*

Allylic substitution using allylic nucleophiles and electrophiles (allyl–allyl coupling) to form 1,5-dienes raises the issue of the allylic regiochemistry on both the nucleophiles and electrophiles, but affords a powerful strategy for C(sp^3)–C(sp^3) bond formation in organic synthesis.[1] In particular, the enantioselective allyl–allyl coupling under the influence of chiral transition-metal catalysts serves as an efficient entry to chiral 1,5-dienes with a stereogenic center at the allylic/homoallylic position. 1,5-Dienes are found in many important biologically active molecules and also serve as useful synthetic intermediates because of the versatility of the two alkene functionalities for further transformations.[2] Nevertheless, such enantioselective reactions had been underdeveloped until Morken and co-workers reported the palladium-catalyzed regio- and enantioselective allyl–allyl coupling between substituted allylboronates and (*E*)-allylic carbonates.[3] Remarkably, this palladium catalysis delivered chiral 1,5-dienes containing two adjacent stereogenic centers with high diastereo- and enantioselectivities. More recently, Feringa and co-workers reported the copper-catalyzed enantioselective coupling between allylmagnesium bromide and (*E*)-allyl bromides, but the S_N2'-type regioselectivity was moderate.[4] Carreira and co-workers developed the irridium-catalyzed regio- and enantioselective coupling between allylsilanes and secondary aromatic allylic alcohols.[5] Despite these efforts, the allyl–allyl coupling using either acyclic or cyclic allylic electrophiles involving a *Z*-alkene moiety is yet to be explored.

Herein, we report copper-catalyzed enantioselective allyl–allyl coupling between allylboronates and (*Z*)-allylic phosphates using a new chiral N-heterocyclic carbene (NHC) ligand bearing a phenolic hydroxy group.[6–8] This reaction occurred with exceptional S_N2'-type regioselectivity and high enantioselectivities to deliver chiral 1,5-diene derivatives with a tertiary carbon stereogenic center at the allylic/homoallylic position. Acid- or base-sensitive functional groups were compatible with this enantioselective reaction. *Z*-Aliphatic allylic substrates including acyclic and cyclic 2-alkene-1,4-diol derivatives can be used. In this regard, the present copper-catalyzed system is complementary to Morken's palladium system, which was applied to primary *E*-allylic electrophiles. Importantly, this study demonstrated that the phenol/NHC chiral ligands have utility not only in the reaction of pronucleophiles with C(sp)–H or C(sp^2)–H bonds but also in those of organoboron compounds.[9]

Earlier, we reported enantioselective S_N2'-type allylic substitution reactions between non-allylic alkylboron (alkyl-9-BBN) compounds and achiral primary allylic substrates under the influence of a catalytic amount of a copper(I) complex and a stoichiometric potassium alkoxide base.[10] On the basis of this knowledge, we developed an unprecedented copper-catalyzed enantioselective allylic substitution with allylboron compounds. In the screening of the reaction conditions, we used readily available allylboronic acid pinacolate esters instead of the allyl-9-BBN reagents (Table 1).[11] In studies aimed toward finding achiral copper systems which enable the selective formation of the racemic, branched γ-substitution product **3aa**, we found that a Cu/NHC (SIMes) complex, prepared in situ from 1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride (SIMes·HCl), CuCl, and KOMe, gave exclusive γ-selectivity (γ/α > 99:1) in the reaction between 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1a**) and the *Z*-allylic phosphate **2a** in THF at −20 °C to form the branched allyl–allyl coupling product (*R*)-**3aa** in high yield (93%; entry 1). In contrast to the excellent ligand performance of the ring-saturated NHC ligand SIMes, the corresponding unsaturated NHC ligand IMes, which is derived from 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl), gave a mixture of branched and linear products with a low γ/α regioselectivity (62:38) in a moderate total product yield (entry 2). The reaction either without a ligand or with 1,10-phenanthroline (Phen) or DPPE ligands did not proceed at all (entries 3–5). Monodentate phosphine ligands such as Ph_3P gave the linear α-substitution product (*E*)-**4aa** exclusively (entry 6).

Based on these results, we decided to investigate various ring-saturated chiral NHC ligands (Table 1, entries 7–14). The C_2-symmetric NHC ligand (*S*,*S*)-**L1**,[12] which has two stereogenic carbon centers in the imidazolidine ring with two N-mesityl groups, gave nearly racemic **3aa** with exclusive γ-regioselectivity and moderate product yield (entry 7).

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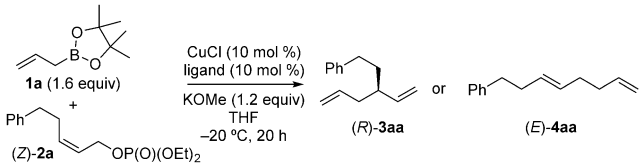
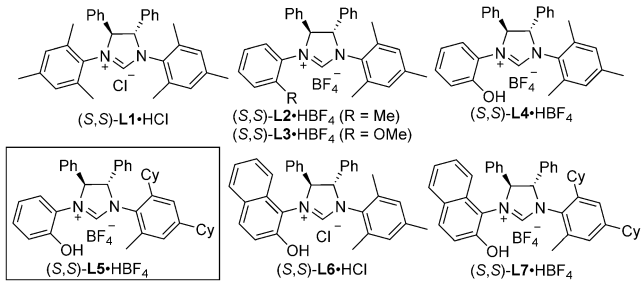
Table 1: Ligand effects in reaction between **1a** and (*Z*)-**2a**.[a]



Entry	Ligand	*T* [°C]	Yield [%][b]	γ/α (**3aa**/**4aa**)[c]	*ee* [%][d]
1	SIMes	−20	93	>99:1	–
2	IMes	−20	65	62:38	–
3	none	−20	0	–	–
4	Phen	−20	0	–	–
5	DPPE	−20	0	–	–
6	PPh_3	−20	57	1:>99	–
7	(*S*,*S*)-**L1**	−20	49	>99:1	2
8	(*S*,*S*)-**L2**	−20	13	>99:1	50
9	(*S*,*S*)-**L3**	−20	10	>99:1	54
10	(*S*,*S*)-**L4**	−20	77	>99:1	85
11	(*S*,*S*)-**L5**	−20	83	>99:1	92
12[e]	(*S*,*S*)-**L5**	−40	80	>99:1	99
13	(*S*,*S*)-**L6**	−20	34	92:8	67
14	(*S*,*S*)-**L7**	−20	56	>99:1	82

[a] Reaction conditions: **1a** (0.24 mmol), (*Z*)-**2a** (0.15 mmol), CuCl/ligand (10 mol%), KOMe (0.18 mmol), THF (0.6 mL) for 20 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The *ee* value was determined by HPLC analysis. [e] **1a** (1.9 mmol) and (*Z*)-**2a** (1.2 mmol) were used. The reaction was carried out for 48 h. DPPE = 1,2-bis(diphenylphosphino)ethane, THF = tetrahydrofuran.



Similar chiral NHC ligands bearing either 2-methylphenyl [(*S*,*S*)-**L2**)] or 2-methoxyphenyl [(*S*,*S*)-**L3**] groups, instead of one of the mesityl groups in (*S*,*S*)-**L1,** induced moderate enantioselectivities, but yields were low (entries 8 and 9). Next, we used the NHC ligand (*S*,*S*)-**L4** bearing a 2-hydroxyphenyl group, which exhibited high ligand performance in the enantioselective copper-catalyzed allylic substitutions with terminal alkyne pronucleophiles, as we reported previously (entry 10).[9a] To our delight, the Cu/(*S*,*S*)-**L4** catalyst system gave higher product yield (77%) and enantioselectivity (85% *ee*) than the system with either (*S*,*S*)-**L2** or (*S*,*S*)-**L3**, and the exclusive regioselectivity was unchanged. This result suggests a functional role of the phenolic hydroxy group in **L4**. Changing the *N*-mesityl group of (*S*,*S*)-**L4** to an *N*-2,4-dicyclohexyl-6-methylphenyl group to afford the new phenol/NHC chiral ligand (*S*,*S*)-**L5** gave even better enantioselectivity with exceptional regioselectivity (γ/α > 99:1) and high yield (entry 11). Furthermore, the enantioselectivity jumped to 99% *ee* by decreasing the reaction temperature to −40 °C (entry 12). However, the naphthol/NHC chiral ligands (*S*,*S*)-**L6** and (*S*,*S*)-**L7**[9b] did not lead to improvement of the enantioselectivity (entries 13 and 14).

Effects of leaving groups and bases are summarized in Table 2. Changing the leaving group to either a bromide or chloride under the reaction conditions used in entry 11 of Table 1, caused a decrease in the γ-regioselectivity and enantioselectivity (Table 2, entries 2 and 3).

Table 2: Effects of leaving groups and bases.[a]

Entry	Leaving group	Base	Yield [%][b]	γ/α (**3aa**/**4aa**)[c]	*ee* [%][d]
1[e]	$OP(O)(OEt)_2$ ((*Z*)-**2a**)	KOMe	83	>99:1	92
2	Cl[f]	KOMe	89	94:6	64
3	Br[g]	KOMe	85	82:18	20
4	$OP(O)(OEt)_2$ ((*Z*)-**2a**)	NaOMe	91	89:11	74
5	$OP(O)(OEt)_2$ ((*Z*)-**2a**)	LiOMe	0	–	–
6	$OP(O)(OEt)_2$ ((*Z*)-**2a**)	KO*t*Bu	67	63:37	50
7	$OP(O)(OEt)_2$ ((*Z*)-**2a**)	K_2CO_3	0	–	–

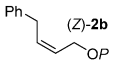
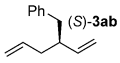
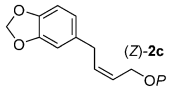
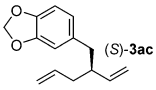
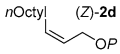
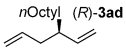
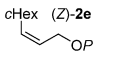
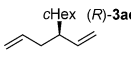
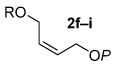
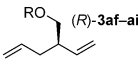
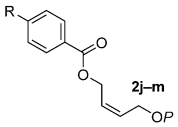
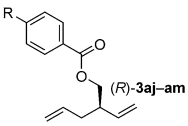
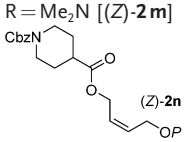
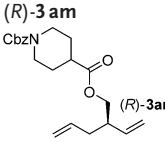
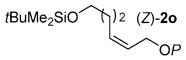
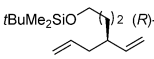
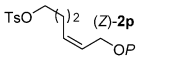
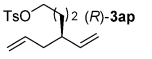
[a] Reaction conditions: **1a** (0.24 mmol), (*Z*)-**2** (0.15 mmol), CuCl/(*S*,*S*)-**L5** (10 mol%), base (0.18 mmol), THF (0.6 mL), −20 °C for 20 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The *ee* value was determined by HPLC analysis. [e] Reraction conditions used in entry 11 of Table 1. [f] (*Z*)-(5-Chloro-3-penten-1-yl)benzene. [g] (*Z*)-(5-Bromo-3-penten-1-yl)benzene.

The nature of the base had a strong impact on the yield, γ-regioselectivity, and enantioselectivity. The use of NaOMe instead of KOMe decreased the regioselectivity and enantioselectivity (entry 4). The use of LiOMe resulted in no reaction (entry 5). The inefficiency of LiOMe may reflect higher solubilities of either LiCl or $LiOP(O)(OEt)_2$, which may form inactive copper species through ionic interactions. The structure of the alkoxide moiety of the base also had a significant impact on the reaction efficiency and selectivity. Thus, when KOMe was changed to a sterically more demanding base, KO*t*Bu, the product yield was moderate and both regioselectivity and enantioselectivity decreased significantly (entry 6). This result suggests that trialkoxyboron ROBpin may participate in the reaction since Lewis acids activate the phosphate leaving group (see Figure 2). No reaction occurred with K_2CO_3 (entry 7).

Z-Allylic phosphates with different aliphatic γ-substituents were subjected to the reaction of **1a** with the Cu/(*S*,*S*)-**L5** catalyst system (Table 3). The 2-phenylethyl group of (*Z*)-**2a** could be replaced with either benzyl or octyl groups and excellent γ-selectivities without a significant decrease in the enantioselectivies (entries 1 and 3). A sterically more demanding γ-substituent, such as a cyclohexyl group ,was also tolerated with the high level of enantioselectivity retained (entry 4).[13] Notably, the enantioselective reaction with 2-butene-1,4-diol derivatives, which have two potential leaving groups at different allylic positions, proceeded with the allylic C−O bonds in either the ether or carboxylic ester leaving groups untouched (entries 5–13).

Various functional groups were tolerated (entries 2 and 5–15). For example, allylic phosphates bearing 1,3-benzodioxole [(*Z*)-**2c**], THP ether [(*Z*)-**2f**], benzyl ether [(*Z*)-**2g**], silyl

Table 3: Scope with respect to the allylic phosphates.[a]

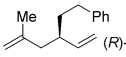
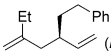
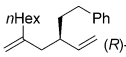
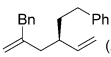
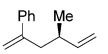
Entry	Phosphate (**2**)	**3**	*T* [°C]	Yield [%][b,c]	*ee* [%][d]
1	 (*Z*)-**2b**	 (*S*)-**3ab**	−50	62	86
2	 (*Z*)-**2c**	 (*S*)-**3ac**	−30	97	86
3	 (*Z*)-**2d**	 (*R*)-**3ad**	−40	85	84
4	 (*Z*)-**2e**	 (*R*)-**3ae**	−50	59	80
	 **2f–i**	 (*R*)-**3af–ai**			
5	R = THP [(*Z*)-**2f**]	(*R*)-**3af**	−30	83	90
6	R = Bn [(*Z*)-**2g**]	(*R*)-**3ag**	−50	75	85
7	R = *t*BuMe$_2$Si [(*Z*)-**2h**]	(*R*)-**3ah**	−50	78	97
8	R = Piv [(*Z*)-**2i**]	(*R*)-**3ai**	−30	70	91
	 **2j–m**	 (*R*)-**3aj–am**			
9	R = MeO [(*Z*)-**2j**]	(*R*)-**3aj**	−30	85	92
10	R = F$_3$C [(*Z*)-**2k**]	(*R*)-**3ak**	−30	61	90
11	R = Br [(*Z*)-**2l**]	(*R*)-**3al**	−30	65	90
12	R = Me$_2$N [(*Z*)-**2m**]	(*R*)-**3am**	−30	87	91
13	 (*Z*)-**2n**	 (*R*)-**3an**	−30	80	90
14	 (*Z*)-**2o**	 (*R*)-**3ao**	−40	78	96
15	 (*Z*)-**2p**	 (*R*)-**3ap**	−30	88	92

[a] Reaction conditions: **1a** (0.24 mmol), (*Z*)-**2** (0.15 mmol), CuCl/(*S,S*)-**L5** (10 mol%), KOMe (0.18 mmol), THF (0.6 mL) for 48 h. [b] Yield of isolated product. [c] Constitutional isomer ratio γ/α > 20:1 (determined by ^{1}H NMR analysis of the crude reaction mixture). [d] The *ee* value was determined by HPLC analysis. Cbz = benzyloxycarbonyl, *OP* = OP(O)(OEt)$_2$, THP = tetrahydropyran, Ts = 4-toluenesulfonyl.

ether [(*Z*)-**2h,o**],[13] pivalate [(*Z*)-**2i**], and *p*-toluenesulfonate [(*Z*)-**2p**] groups as the aliphatic γ-substituent reacted to afford the corresponding 1,5-diene products in good yields with high enantioselectivities (entries 2, 5–8, 14 and 15). Methoxy, trifluoromethyl, bromo, and dimethylamino substituents on the aromatic ring of the benzoate groups were tolerated (entries 9–12). A carbamate group was compatible with this enantioselective reaction (entry 13).

The reactions of β-substituted allylboronate derivatives were examined with the Cu/(*S,S*)-**L5** catalyst system (Table 4). Methallylboronate (**1b**) and 2-ethyl-2-propen-1-ylboronate (**1c**) reacted with (*Z*)-**2a** with excellent γ-selectivity and with high enantioselectivities (entries 1 and 2). Allylboronate derivatives (**1d–f**) with hexyl, benzyl, and phenyl groups at the β-position underwent the coupling to

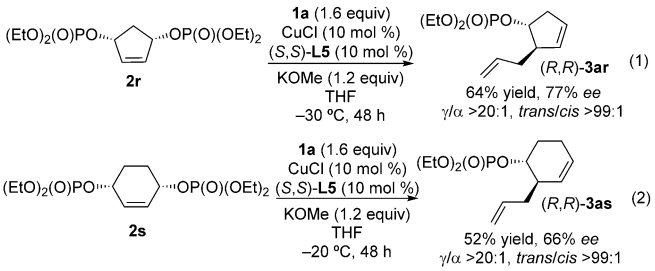
Table 4: Scope with respect to the allylboronates.[a]

Entry	Allylboronate	(*Z*)-**2**	Product	Yield [%][b]	γ/α[c]	*ee* [%][d]
1	 **1b**	(*Z*)-**2a**	 (*R*)-**3ba**	77	> 20:1	95
2	 **1c**	(*Z*)-**2a**	 (*R*)-**3ca**	50	> 20:1	80
3	 **1d**	(*Z*)-**2a**	 (*R*)-**3da**	87	84:16	80
4	 **1e**	(*Z*)-**2a**	 (*R*)-**3ea**	59	87:13	82
5	 **1f**	 (*Z*)-**2q**	 (*R*)-**3fq**	89	78:22	83

[a] Reaction conditions: **1** (0.24 mmol), (*Z*)-**2** (0.15 mmol), CuCl/(*S,S*)-**L5** (10 mol%), KOMe (0.18 mmol), THF (0.6 mL), −50°C (entry 1) or −30°C (entries 2–5) for 48 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The *ee* value was determined by HPLC analysis. *OP* = OP(O)(OEt)$_2$.

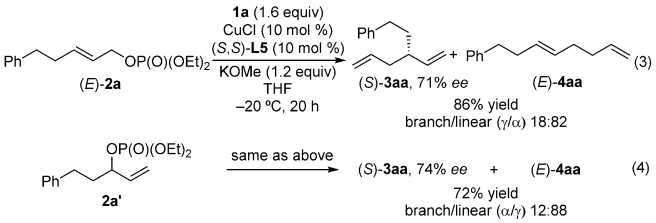
give the corresponding chiral 1,5-dienes with enantiomeric excesses over 80%, while the γ-selectivities were moderate (entries 3–5).[14] Unfortunately, γ-substituted allylborons such as *trans*- or *cis*-crotylboronates did not react under identical reaction conditions.

The coupling between **1a** and *cis*-4-cyclopentene-1,3-diol diphosphate (*Z*)-**2r** catalyzed by Cu/(*S,S*)-**L5** system occurred with a useful level of enantioselectivity, thus giving the *trans*-1,2-isomer **3ar** [Eq. (1)].[13] The reaction with the *cis*-4-cyclohexene-1,3-diol derivative (*Z*)-**2s** afforded the *trans*-1,2-isomer **3as** with moderate enantiocontrol [Eq. (2)]. These stereochemical outcomes indicate that the present copper-catalyzed reaction proceeded through an *anti*-S$_N$2′-type reaction pathway. Notably, Morken's palladium-catalyzed protocol has not been applied to this type of cyclic allylic electrophile involving a *Z*-alkene moiety.[3]



The alkene geometry of the allylic phosphates had a strong impact on both the regioselectivity and enantioselectivity. Thus, the reaction between **1a** and (*E*)-**2a** under the reaction conditions used for entry 11 in Table 1, afforded the linear α-substitution product (*E*)-**4aa** as a major product together with a minor formation of (*S*)-**3aa**, the antipode of the product derived from (*Z*)-**2a** [Eq. (3)]. This α-substitution product (*E*)-**4aa** seemed to be produced by allylic 1,3-migration of copper in the allylcopper(III) species. To gain deeper insight into the nature of the postulated allylcopper(III) species, we conducted the reaction of the secondary

allylic phosphate **2a"**, a constitutional isomer of (*Z*)-**2a** [Eq. (4)]. Interestingly, this reaction gave almost the same product distribution as the reaction with (*E*)-**2a**. The



observed convergency in the regioselectivity and stereochemical outcome suggest that (*E*)-**2a** and **2a"** lead to a common equilibrium mixture of the allylcopper(III) species prior to reductive elimination to form the product mixture (Figure 1).[15]

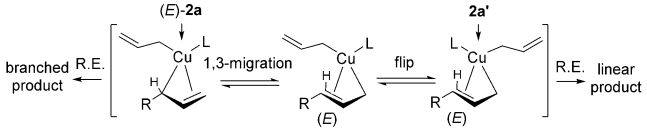


Figure 1. Allylcopper(III) species.

Based on the assumption that the γ-selective reaction of (*Z*)-**2** also occurs via allylcopper(III) intermediates, we postulated a catalytic reaction pathway for the enantioselective allyl–allyl coupling catalyzed by Cu/(*S*,*S*)-**L5**, as shown in Figure 2.[15] The reaction of CuCl, (*S*,*S*)-**L5**, and KOMe forms an alkoxycopper(I) complex (**A**), in which the chiral NHC ligand coordinates to Cu as an anionic C,O-bidentate ligand. Next, transmetalation between **A** and an allylborate (**B**)[16] produces a potassium phenoxo(allyl)cuprate (**C**). **C** forms a π-complex (**D**) with the allylic phosphate **2**, in which Cu is *anti* to the phosphate leaving group, which may be activated through participation of MeOBpin Lewis acid.[10d] Subsequently, the oxidative addition forms the (π-en-σ-yl)copper(III) complex **E1** with a secondary sp^3-carbon atom bound to Cu. Facile reductive elimination of **E1** is faster than allylic 1,3-Cu-migration to form **E2**, and thus produces the branched γ-substitution product **3** and regenerates **A** for the next catalytic cycle (see the Supporting Information for enantiodiscrimination models).

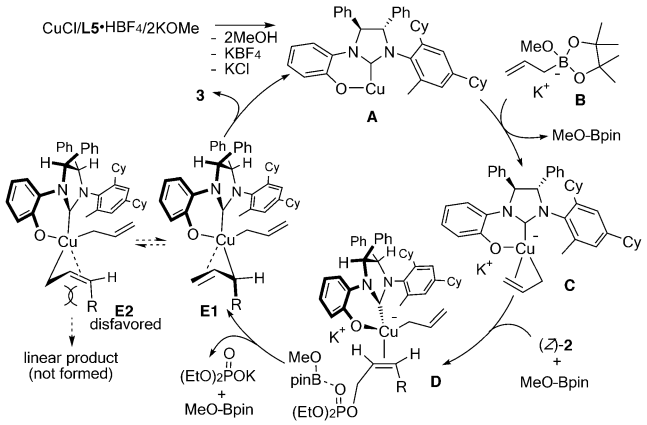


Figure 2. Postulated catalytic reaction pathway.

Based on this assumption, the crucial dependence of the regioselectivity on the *E*/*Z* geometry of the allylic substrate (**2**) can be explained by higher instability of **E2**, compared to the corresponding Cu^{III} species produced from the *E* substrate, because of greater steric repulsion in the allyl moiety derived from the *Z* substrate (see Figure 1). In this regard, **E1** may be better described as a (η^1-allyl)copper(III) complex without alkene coordination.

In summary, we have developed the enantioselective S_N2'-type allyl–allyl coupling between allylboronates and *Z*-acyclic and cyclic allylic phosphates. This coupling was enabled by catalysis of a copper(I) complex with a new phenol/NHC chiral ligand, thus demonstrating the utility of this class of chiral ligands for enantioselective copper catalysis with organoboron compounds.[9] Various functional groups are tolerated in the aliphatic allylic phosphates. This copper-catalyzed protocol provides efficient access to functionalized, enantioenriched chiral 1,5-dienes with a tertiary carbon stereogenic center at the allylic/homoallylic position, which can be further applied in the synthesis of complex molecules. The broad functional-group compatibility and the use of earth-abundant and relatively low toxicity copper as a metal are attractive features of this protocol.

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[14] The linear α-substitution product was the *E* isomer.
[15] Nakamura and co-workers conducted DFT calculations on the mechanism of the reaction between [MeCu(CN)Li] and allyl acetate to form a square planar four-coordinate (γ-*σ*-enyl)copper(III) species [(π-en-σ-yl)copper(III) complex]. Our mechanistic proposal is in accord with the Nakamura's mechanism, in which the (γ-*σ*-enyl)copper(III) species is not in equilibrium with the corresponding (α-*σ*-enyl)coppor(III) species. The regioselectivity is determined at the oxidative addition step as a consequence of the asymmetric nature of $MeCuCN^-$. Our proposed mechanism is in accord with the Nakamura's mechanism in that the reaction proceeds through oxidative addition of a cuprate to form the (γ-*σ*-enyl)copper(III) species followed by reductive elimination. However, the coordination number of Cu in the allylcopper(III) complex is different by virtue of bidentate coordination of the anionic phenol/NHC chiral ligand (L). The strongly electron-donating NHC coordination should render the π–en coordination weaker, thus making the allylic 1,3-copper migration in the allylcopper(III) complex more feasible. See: a) N. Yoshikai, S.-L. Zhang, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 1286. For the effect of a σ-donor ligand, see: b) M. Yamanaka, S. Kato, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 6287.
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