Synthesis Y. Yasuda et al. Paper

Copper-Catalyzed Enantioselective Coupling between Allylboronates and Phosphates Using a Phenol–Carbene Chiral Ligand: Asymmetric Synthesis of Chiral Branched 1,5-Dienes

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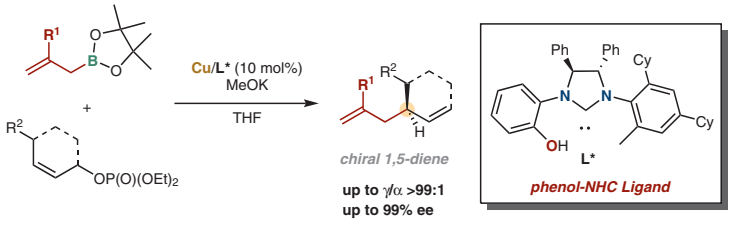

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Abstract Details of the Cu-catalyzed enantioselective allyl–allyl coupling reaction between allylboronates and (*Z*)-allylic phosphates using a new chiral *N*-heterocyclic carbene (NHC) ligand containing a phenolic hydroxy group are presented. The copper catalysis delivers enantioenriched chiral 1,5-dienes with a tertiary stereogenic center. Compatibility with various functional groups and the use of earth-abundant and relatively low-toxicity copper as a metal are attractive features of this protocol. The utility of the chiral phenol–NHC ligand for enantioselective copper catalysis with organoboron compounds is demonstrated and enantiodiscrimination models are discussed.

Key words asymmetric catalysis, allylic substitution, synthetic methods copper catalysis, organoboron compounds

Chiral 1,5-dienes with a stereogenic center at the allylic/homoallylic position are found in many important biologically active molecules, such as FK-506, plakortide E, and chaetoglobosin A (Figure 1),[1] and also serve as useful building blocks in organic synthesis due to the versatility of the two alkene functionalities for further transformations. While several methods have been developed to produce chiral 1,5-dienes,[2] enantioselective γ-substitution of allyl alcohol derivatives with organometal reagents (allyl–allyl coupling) using chiral transition-metal complexes as catalysts is the most straightforward because it uses readily available substrates.[3]

In 2010, Morken and co-workers reported the pioneering example of catalytic asymmetric allyl–allyl coupling; Pd-catalyzed allyl–allyl coupling between substituted allylboronates4 and (*E*)-allylic carbonates occurred with high regio- and enantioselectivity.[5] This protocol enabled access to chiral 1,5-dienes containing contiguous stereogenic centers with high diastereo- and enantioselectivity. More recently, Feringa's group reported asymmetric cross-coupling between allyl Grignard reagents and (*E*)-allyl bromides using a copper–chiral monodentate phosphoramidite catalyst, but only moderate S_N2' regioselectivity was obtained.[6] In 2014, Carreira and co-workers developed Ir-catalyzed regio- and enantioselective allylic cross-coupling between allylsilanes and secondary aromatic allylic alcohols.[7] Despite these efforts, allyl–allyl coupling was limited to the use of acyclic (*E*)-allylic electrophiles.

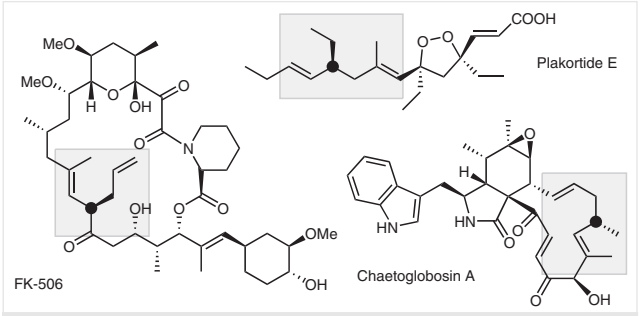
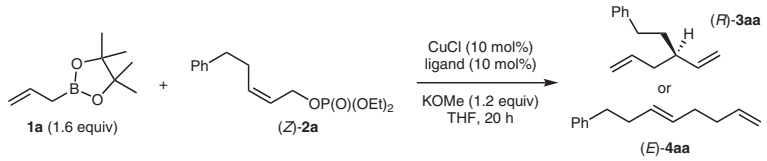


Figure 1 Biologically active compounds

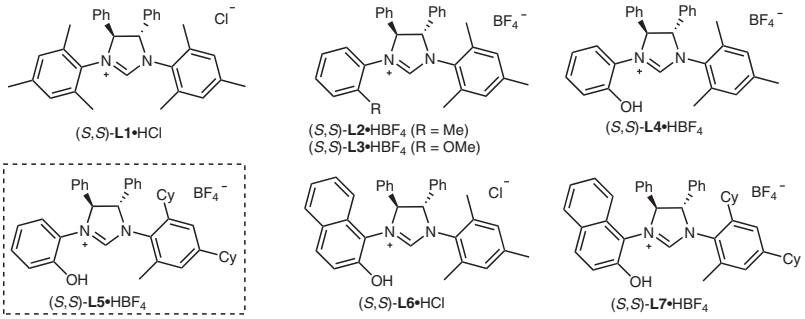
Recently, the Cu-catalyzed enantioselective allyl–allyl coupling between allylboronates and allylic phosphates[8–11] using a new chiral *N*-heterocyclic carbene (NHC) ligand bearing a phenolic hydroxy group[12,13] was reported. Reaction occurred with exceptional γ-regioselectivity and high enantioselectivity. Various functional groups were tolerated. The ability to use (*Z*)-aliphatic allylic substrates in the copper catalysis was complementary to Morken's Pd system (in their reports, only primary (*E*)-allylic electrophiles were used).[5] The present report describes the details of further studies of this Cu-catalyzed enantioselective allyl–allyl coupling.[8]

Enantioselective S_N2' allylic alkylation between non-allylic alkylboranes (alkyl-9-BBN) and primary allylic substrates using a catalytic amount of a chiral bisphosphine/copper(I) complex and a stoichiometric amount of potassium alkoxide base has been reported.[14] The results prompted the initiation of a program to develop a Cu-catalyzed enantioselective allylic substitution with allylboron reagents. For screening of the reaction conditions, commercially available allylboronic acid pinacol esters were used instead of the allyl-9-BBN reagents (Table 1).[15] During investigation of an effective achiral ligand that could selectively produce the racemic, branched γ-substitution product **3aa**, a ring-saturated NHC/copper complex, prepared *in situ* from 1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride (SIMes·HCl), CuCl, and KOMe, produced coupling product **3aa** in high yield (93%) with exclusive γ-regioselectivity (γ/α >99:1) from the reaction between 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1a**) and γ-monosubstituted primary (*Z*)-allylic phosphate **2a** in THF at –20 °C (entry 1). In contrast to the excellent performance of the ring-saturated NHC ligand SIMes, the corresponding unsaturated NHC ligand IMes, 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) and moderate total product yield (entry 2). Without a ligand, or with 1,10-phenanthroline (Phen) or 1,2-bis(diphenylphosphino)ethane (DPPE) as the ligand, no reaction occurred (entries 3–5). The use of triphenylphosphine (Ph_3P) as a monodentate phosphine ligand gave only the linear α-substitution product (*E*)-**4aa** (entry 6).

Table 1 Ligand Effects in the Reaction between **1a** and (*Z*)-**2a**[a]



Entry	Ligand	Temp (°C)	Yield (%)[b]	γ/α (**3aa**/**4aa**)[c]	ee (%)[d]
1	SIMes·HCl	–20	93	>99:1	–
2	IMes·HCl	–20	65	62:38	–
3	none	–20	0	–	–
4	Phen	–20	0	–	–
5	DPPE	–20	0	–	–
6	Ph_3P	–20	57	1:>99	–
7	(*S*,*S*)-**L1**·HCl	–20	49	>99:1	2
8	(*S*,*S*)-**L2**·HBF_4	–20	13	>99:1	50
9	(*S*,*S*)-**L3**·HBF_4	–20	10	>99:1	54
10	(*S*,*S*)-**L4**·HBF_4	–20	77	>99:1	85
11	(*S*,*S*)-**L5**·HBF_4	–20	83	>99:1	92
12[e]	(*S*,*S*)-**L5**·HBF_4	–40	80	>99:1	99
13	(*S*,*S*)-**L6**·HCl	–20	34	92:8	67
14	(*S*,*S*)-**L7**·HBF_4	–20	56	>99:1	82



[a] Data are taken from ref. 8. Reaction conditions: **1a** (0.24 mmol), (*Z*)-**2a** (0.15 mmol), CuCl/ligand (10 mol%), KOMe (0.18 mmol), THF (0.6 mL), 20 h.
[b] Yield of isolated product.
[c] Determined by ^1H NMR analysis of crude product.
[d] The ee was determined by HPLC.
[e] **1a** (1.9 mmol) and (*Z*)-**2a** (1.2 mmol) were used. Reaction was conducted for 48 h.

Based on these results, focus was placed on ring-saturated chiral NHC ligands (Table 1, entries 7–14). The C_2-symmetric imidazolinium chloride (*S*,*S*)-**L1**·HCl,[16] which has two stereogenic carbon centers in the imidazolidine ring with two *N*-mesityl groups, did not result in enantioselectivity; the branched, nearly racemic coupling product **3aa** was obtained with exclusive regioselectivity and moderate yield (entry 7). When similar chiral NHC ligands bearing a 2-methylphenyl (**L2**) or 2-methoxyphenyl (**L3**) group, instead of one of the mesityl groups in **L1**, were used enantioselectivity was moderate (50% and 54% ee), but yields were low (entries 8 and 9). Next, the imidazolinium salt **L4**·HBF_4 bearing a 2-hydroxyphenyl group was used (entry 10). A previous report indicated that **L4** exhibited high ligand performance in enantioselective Cu-catalyzed allylic substitution with terminal alkynes as pronucleophiles.[12a] Fortunately, the Cu/**L4** catalyst system produced better results; the coupling product was formed in greater yield (77%) and with greater enantioselectivity (85% ee) compared to the system using (*S*,*S*)-**L2** or **L3**, without decreasing regioselectivity. These results indicated that the phenolic hydroxy group in **L4** has a functional role. Changing the *N*-mesityl group of **L4**·HBF_4 to an *N*-2,4-dicyclohexyl-6-methylphenyl group to afford the new phenol–NHC chiral ligand precursor **L5**·HBF_4 resulted in greater enantioselectivity (92% ee), a high yield (83%), and exceptional regioselectivity (γ/α >99:1) (entry 11). Furthermore, higher enantioselectivity was achieved (99% ee) by decreasing the reaction temperature to –40 °C (entry 12). In contrast, the naphthol–NHC chiral ligands **L6** and **L7**[12b] were not effective (entries 13 and 14).

Table 2 Effects of Copper Salt and Solvent[a]

Entry	Copper salt	Solvent	Yield (%)[b]	γ/α [(*R*)-**3aa**/(*E*)-**4aa**][c]	ee (%)[d]
1[e]	CuCl	THF	83	>99:1	92
2	CuOAc	THF	85	91:9	76
3	$Cu(OAc)_2$	THF	68	73:27	52
4	CuOTf·toluene$_{1/2}$	THF	48	>99:1	90
5	MesCu	THF	85	>99:1	89
6	$Cu(MeCN)_4PF_6$	THF	73	>99:1	88
7	CuCl	toluene	43	64:36	0
8	CuCl	DCM	26	71:29	51
9	CuCl	MeCN	0	–	–
10	CuCl	hexane	0	–	–

[a] Reaction conditions: **1a** (0.24 mmol), (*Z*)-**2a** (0.15 mmol), Cu salt/(*S*,*S*)-**L5**·HBF_4 (10 mol%), KOMe (0.18 mmol), solvent (0.6 mL), –20 °C, 20 h.
[b] Yield of isolated product.
[c] Determined by ^{1}H NMR analysis of crude product.
[d] The ee was determined by HPLC.
[e] Table 1, entry 11.

Next, the effect of the copper salt (Table 2) was investigated. When CuOAc was used as the catalyst, the regioselectivity (γ/α 91:9) and enantioselectivity (76% ee) decreased (entry 2). The use of $Cu(OAc)_2$, instead of copper(I) salt, resulted in a modest yield and low selectivities (entry 3). Changing CuCl to CuOTf·toluene$_{1/2}$ afforded similar selectivity, but a lower product yield (entry 4). Use of MesCu and cationic $Cu(MeCN)_4PF_6$ was as effective as CuCl, and gave comparable results (entries 5 and 6).

The effect of solvent is also shown in Table 2. Reaction in toluene (entry 7) gave only the racemic product in moderate yield (43%) and low regioselectivity (γ/α 64:36). Dichloromethane was ineffective in the reaction (26% yield, γ/α 71:29, 51% ee) (entry 8). No reaction occurred in acetonitrile or hexane (entries 9 and 10).

The effects of the leaving group and base are summarized in Table 3. The use of an allyl bromide or chloride as the allylic electrophile under the conditions described for Table 1, entry 11, decreased both regio- and enantioselectivity (entries 2 and 3).

The nature of the base had a significant impact on yield and selectivities (Table 3). Use of NaOMe instead of KOMe decreased regioselectivity (γ/α 89:11) and enantioselectivity (74% ee) (entry 4). No reaction occurred with LiOMe, due to the greater solubility of LiCl or $LiOP(O)(OEt)_2$, which may form inactive copper species through ionic interactions (entry 5). The structure of the alkoxide moiety of the base also had a strong impact on yield, regioselectivity, and enantioselectivity. Thus, when KOMe was changed to a sterically more demanding base, KO*t*-Bu, product yield was moderate and both regioselectivity and enantioselectivity decreased significantly (entry 6). This result suggests that the trialkoxyboron ROBpin may participate in the reaction

Table 3 Effects of Leaving Group and Base[a]

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

[a] Data are taken from ref. 8. Reaction conditions: **1a** (0.24 mmol), (*Z*)-**2** (0.15 mmol), CuCl/(*S*,*S*)-**L5**·HBF_4 (10 mol%), base (0.18 mmol), THF (0.6 mL), –20 °C, 20 h.
[b] Yield of isolated product.
[c] Determined by ^{1}H NMR analysis of crude product.
[d] The ee was determined by HPLC.
[e] Table 1, entry 11.
[f] (*Z*)-(5-Chloro-3-penten-1-yl)benzene.
[g] (*Z*)-(5-Bromo-3-penten-1-yl)benzene.

because Lewis acids activate the phosphate leaving group (see Scheme 7). The coupling reaction did not occur with K_2CO_3 (entry 7).

Once the optimization of the reaction conditions was implemented, the substrate scope was investigated. (*Z*)-Allylic phosphates with various aliphatic substituents were reacted with **1a** using the Cu/**L5** catalyst system (Table 4). When the 2-phenylethyl group of **2a** was replaced with a benzyl or octyl group, coupling proceeded with excellent γ-selectivity and preservation of enantioselectivity (entries 1 and 3). A sterically more demanding γ-substituent, such as a cyclohexyl group, was also tolerated and produced a high level of enantioselectivity (80% ee) (entry 4).[17] Notably, the enantioselective reaction with 2-butene-1,4-diol derivatives, which have two potential leaving groups at different allylic positions, occurred with the allylic C–O bond in the ether or carboxylic ester leaving group untouched (entries 5–12 and 15).

The reaction has a broad functional group compatibility (entries 2 and 5–12, 15–17). For example, allylic phosphates bearing a 1,3-benzodioxole (**2c**), THP ether (**2f**), benzyl ether (**2g**), silyl ether (**2h**, **2q**),[17] pivalate (**2i**), carbamate (**2p**), or *p*-toluenesulfonate (**2r**) group as a component of the aliphatic γ-substituent reacted with **1a** to produce the corresponding 1,5-diene derivatives in good yields with high enantioselectivities (85–97% ee) (entries 2, 5–8, 15–17). A methoxy, trifluoromethyl, bromo, or dimethylamino substituent was tolerated in the aromatic ring of a benzoate group (entries 9–12). However, no reaction occurred with the allylic phosphates bearing a nitro (**2n**) or cyano (**2o**) group (entries 13 and 14).

Table 4 Scope of Allylic Phosphates[a]

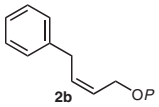
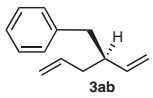
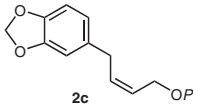
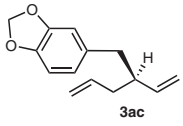
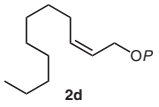
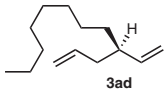
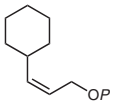
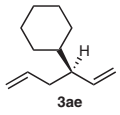
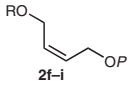
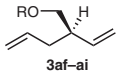
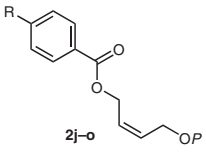
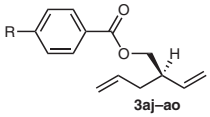
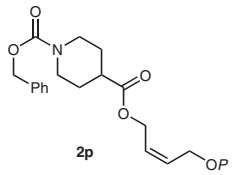
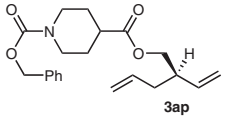
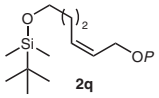
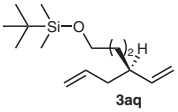
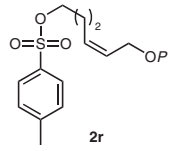
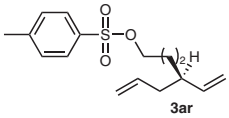
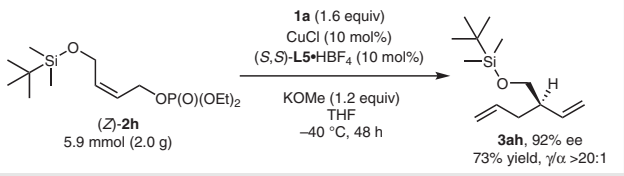
Entry	Phosphate OP = OP(O)(OEt)$_2$	Product	Temp (°C)	Yield (%)[b,c]	ee (%)[d]
1	 **2b**	 **3ab**	–50	62	86
2	 **2c**	 **3ac**	–30	97	86
3	 **2d**	 **3ad**	–40	85	84
4	 **2e**	 **3ae**	–50	59	80
	 **2f–i**	 **3af–ai**			
5	R = THP (**2f**)	**3af**	–30	83	90
6	R = Bn (**2g**)	**3ag**	–50	75	85
7	R = TBS (**2h**)	**3ah**	–50	78	97
8	R = Piv (**2i**)	**3ai**	–30	70	91
	 **2j–o**	 **3aj–ao**			

Table 4 (continued)

Entry	Phosphate *OP* = OP(O)(OEt)$_2$	Product	Temp (°C)	Yield (%)[b,c]	ee (%)[d]
9	R = OMe (**2j**)	**3aj**	–30	85	92
10	R = CF_3 (**2k**)	**3ak**	–30	61	90
11	R = Br (**2l**)	**3al**	–30	65	90
12	R = NMe_2 (**2m**)	**3am**	–30	87	91
13	R = NO_2 (**2n**)	**3an**	–10	0	–
14	R = CN (**2o**)	**3ao**	–10	0	–
15	 **2p**	 **3ap**	–30	80	90
16	 **2q**	 **3aq**	–40	78	96
17	 **2r**	 **3ar**	–30	88	92

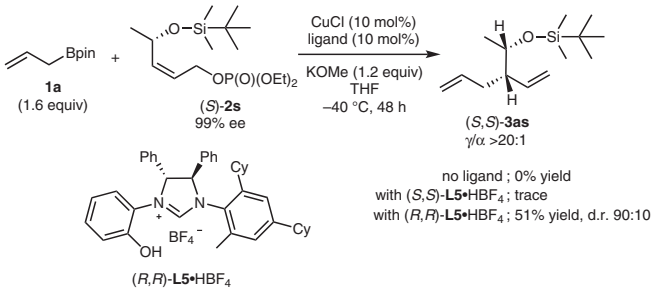
[a] Data for entries 1–12 and 15–17 are taken from ref. 8. Reaction conditions: **1a** (0.24 mmol), (*Z*)-**2** (0.15 mmol), CuCl/(*S*,*S*)-**L5**·HBF_4 (10 mol%), KOMe (0.18 mmol), THF (0.6 mL), 48 h.
[b] Yield of isolated product.
[c] Constitutional isomer ratio γ/α >20:1 (determined by ^{1}H NMR analysis of crude product).
[d] The ee was determined by HPLC.



Scheme 1 Preparative scale reaction

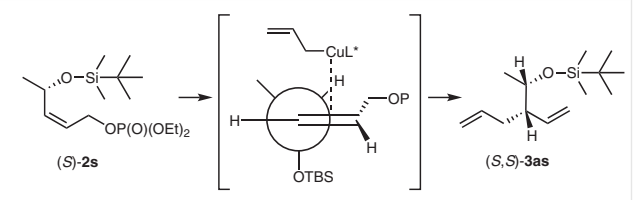
The potential for scaling up the enantioselective allyl–allyl coupling was examined on a preparative scale (Scheme 1). Reaction between allylboronate **1a** (1.5 g, 9.4 mmol) and allylic phosphate **2h** (2.0 g, 5.9 mmol) afforded only the branched coupling product **3ah** in 73% yield (0.98 g, 4.3 mmol) with 92% ee.

The Cu-catalyzed allyl–allyl coupling reaction between **1a** and enantioenriched 2-butene-1,4-diol derivative (*S*)-**2s** (99% ee) with (*R*,*R*)-**L5**·HBF_4 (i.e., enantiomeric isomer of (*S*,*S*)-**L5**·HBF_4) gave the corresponding 1,5-diene **3as** with two adjacent stereogenic centers with an *S*,*S*-configuration in modest yield (51%) and high diastereoselectivity (d.r. 90:10) (Scheme 2). Without a ligand, or with (*S*,*S*)-**L5**·HBF_4, the reaction gave no or only a trace of the coupling product. Thus, the use of **L5** is mandatory, and the (*R*,*R*)-**L5**/Cu system and the (*S*)-**2s** substrate are a matched pair, while (*S*,*S*)-**L5**/Cu complex and (*S*)-**2s** are mismatched. This result is in



Scheme 2 Construction of two adjacent stereogenic centers

accord with a consideration of the Felkin–Anh model as depicted in Scheme 3, which predicts preferred approach of the organocopper nucleophile to the *Si* face of the allylic plane with a minimum $A^{1,3}$ strain.

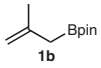
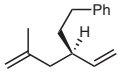
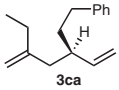
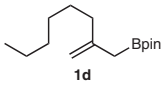
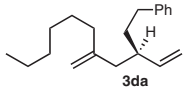
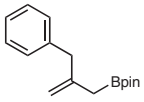
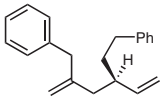
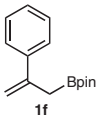
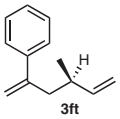
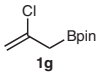
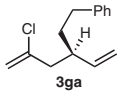


Scheme 3 Felkin–Anh-type stereoselection model

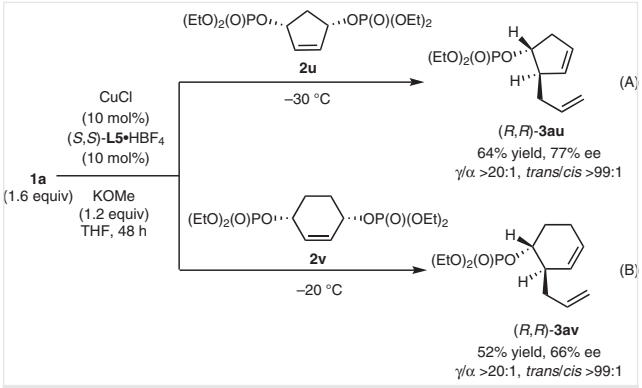
Reactions of β-substituted allylboronate derivatives using the Cu/**L5** catalyst system were investigated (Table 5). Methallylboronate **1b** and 2-ethyl-2-propen-1-ylboronate **1c** reacted with (*Z*)-**2a** with excellent γ-selectivity (γ/α >20:1) and high enantioselectivity (95% and 80% ee, respectively) (entries 1 and 2). Allylboronates **1d–f** with a hexyl, benzyl, or phenyl group at the β-position underwent reaction to afford the coupling products with enantiomeric excesses greater than 80%, while the regioselectivities were moderate (entries 3–5).[18] Allylboronate **1g** with a chloro group at the β-position did not react (entry 6). In addition, no reaction occurred with γ-substituted allylboronates such as *trans*- or *cis*-crotylboronates.

The coupling reaction between **1a** and *cis*-4-cyclopentene-1,3-diol diphosphate **2u** catalyzed by the Cu/**L5** system occurred with adequate enantioselectivity, giving the *trans*-1,2-isomer **3au** (Scheme 4, A).[17,19] Reaction with *cis*-2-cyclohexene-1,4-diol derivative **2v** gave the *trans*-1,2-isomer **3av** with moderate enantiocontrol (66% ee) (Scheme 4, B). These stereochemical results indicate that the present Cu-catalyzed reaction proceeds through an *anti*-S_N2'-type reaction pathway. Morken's Pd-catalyzed protocol has not been applied to this type of cyclic allylic electrophile involving a *Z*-alkene moiety.[5]

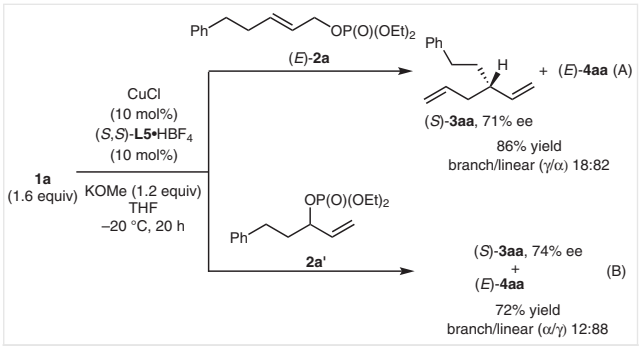
Table 5 Scope of Allylboronates

Entry	Allylboronate	Phosphate OP = $OP(O)(OEt)_2$	Product	Yield (%)[b]	γ/α[c]	ee (%)[d]
1	 **1b**	**2a**	 **3ba**	77	>20:1	95
2	 **1c**	**2a**	 **3ca**	50	>20:1	80
3	 **1d**	**2a**	 **3da**	87	84:16	80
4	 **1e**	**2a**	 **3ea**	59	87:13	82
5	 **1f**	 **2t**	 **3ft**	89	78:22	83
6	 **1g**	**2a**	 **3ga**	0	–	–

[a] Data for entries 1–5 are taken from ref. 8. Reaction conditions: **1** (0.24 mmol), (*Z*)-**2** (0.15 mmol), CuCl/(*S*,*S*)-**L5**·HBF_4 (10 mol%), KOMe (0.18 mmol), THF (0.6 mL), –50 °C (entry 1) or –30 °C (entries 2–6), 48 h.
[b] Yield of isolated product.
[c] Determined by ^{1}H NMR analysis of crude product.
[d] The ee was determined by HPLC.



Scheme 4 Use of cyclic allylic phosphates



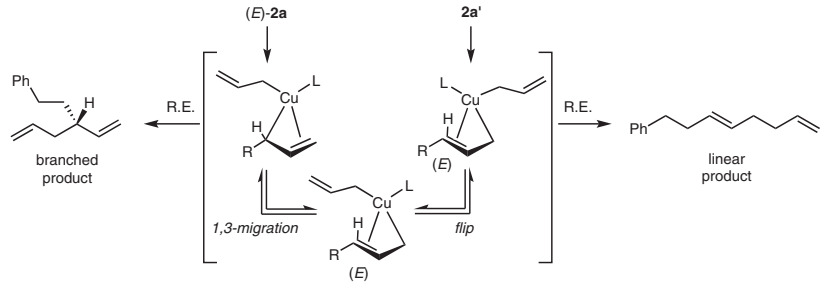
Scheme 5 Reaction of (*E*)-**2a** and **2a'**

In this study we also studied the reaction mechanism and we herein propose a possible reaction pathway. The alkene geometry of the allylic phosphates influences both regio- and enantioselectivity. Thus, reaction between **1a** and (*E*)-**2a** under the conditions described in Table 1, entry 11 gave the linear α-substitution product (*E*)-**4aa** preferentially, with minor formation of (*S*)-**3aa** (71% ee), the antipode of the product derived from (*Z*)-**2a** (Scheme 5, A).[19] This α-selectivity appeared to occur via allylic 1,3-migration of copper in the allylcopper(III) species. To gain insight into the nature of the postulated allylcopper(III) species, secondary allylic phosphate **2a'**, a constitutional isomer of (*Z*)-**2a**, was reacted under the same conditions (Scheme 5, B).[19] Interestingly, this reaction gave results similar to the reaction with (*E*)-**2a**. The convergence observed in the regioselectivity and stereochemistry suggests that (*E*)-**2a** and **2a'** lead to a common equilibrium mixture of the allylcopper(III) species prior to reductive elimination (R.E.) to form the product mixture (Scheme 6).[20]

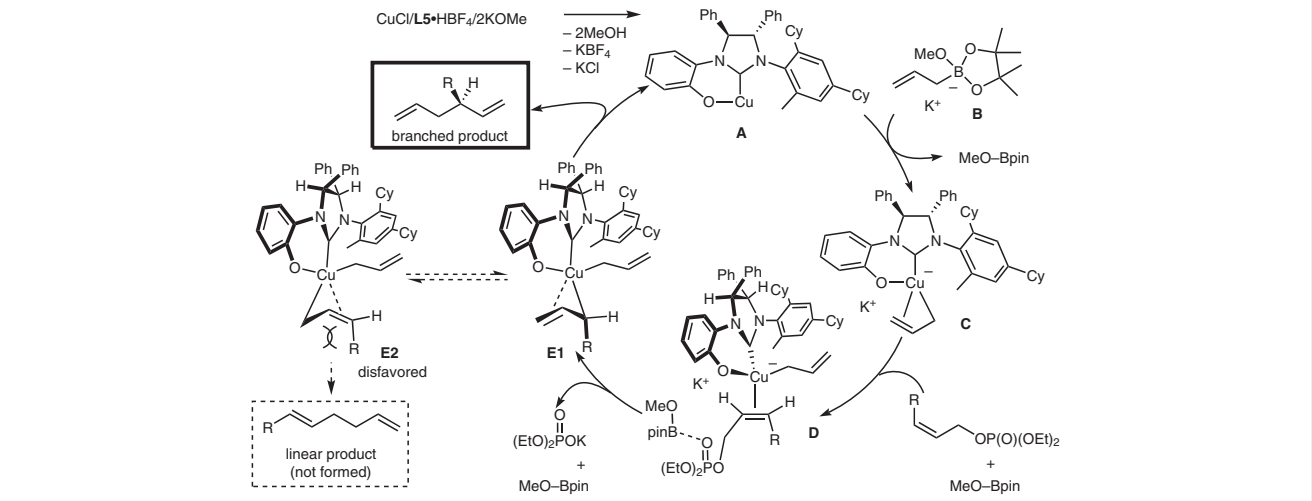
Based on the assumption that the γ-selective reaction of (*Z*)-**2** also occurs via allylcopper(III) intermediates, a catalytic cycle was proposed for the enantioselective allyl–allyl coupling catalyzed by the Cu/**L5** system, as shown in Scheme 7.[20] An alkoxycopper(I) complex **A** is formed from reaction between CuCl, **L5**·HBF_4, and KOMe. For this complex, the chiral NHC ligand coordinates to copper as an anionic C,O-bidentate ligand. Then, transmetalation between **A** and an allylborate **B**[21] affords the potassium phenoxo(allyl)cuprate **C**. Compound **C** forms a π-complex **D** with the allylic phosphate **2**, in which the copper is *anti* to the phosphate leaving group. The MeOBpin may activate the phosphate group as a Lewis acid.[14d] Subsequently, oxidative addition produces (π-en-σ-yl)copper(III) complex **E1** with a secondary sp^3-carbon atom bound to copper. Facile reductive elimination of **E1**, which is faster than allylic 1,3-copper migration to form **E2**, produces the branched γ-substitution product **3** and regenerates the alkoxycopper(I) complex **A** (see Figures 2 and 3 for enantiodiscrimination models).

Thus, the crucial dependence of regioselectivity on the *E*/*Z* geometry of the allylic substrate **2** can be explained by the greater instability of the allylcopper(III) intermediate **E2** compared to the corresponding copper(III) species **E1** produced from the *E*-substrate, due to larger steric repulsion in the allyl moiety derived from the *Z*-substrate (Scheme 6). Similar consideration may be applicable to the corresponding transition states that determine the *E*/*Z*-isomeric product distribution.

Reactions of the *E*- and *Z*-isomers of **2a** gave the antipodes of **3aa** (Table 1, entry 11 vs Scheme 5, A), and the product from (*Z*)-**2a** was produced with greater enantioselectivity. This led to the proposal of the enantioselection models shown in Figures 2 and 3. In the π-complex **D** (Scheme 7), the chiral copper center adopts a tetrahedral coordination geometry including the C,O-bidentate chelation. The K^+ ion bridges the phenoxide oxygen and MeOBpin, which inter-



Scheme 6 Allylcopper(III) species



Scheme 7 Postulated catalytic reaction pathway

acts with the phosphate leaving group as a Lewis acid. These assumptions suggest four possible π-complexes (**D1** and **D2** for the major enantiomer; **D3** and **D4** for the minor enantiomer) (Figure 2). Complex **D1** is the most favorable, because it results in the fewest steric repulsions between catalyst and allylic phosphate. Complexes **D2**, **D3**, and **D4** appear to be destabilized by steric repulsions between the γ-substituent (R) and the non-hydroxylated *N*-aryl group or one of the phenyl groups on the imidazolidine ring. These conclusions are consistent with the experimental observations that the enantioselectivity is influenced by the steric nature of the γ-substituent (R) (Table 4, entries 3 and 4) and the non-hydroxylated *N*-aryl group in the phenolic NHC ligands (Table 1, entries 10 and 11).

For the reaction of (*E*)-**2** (Figure 3), the non-hydroxylated *N*-aryl group and/or the phenyl group on the imidazolidine ring causes steric repulsion toward the γ-substituent (R) for all postulated complexes **D1′–D4′**. These considerations explain the more efficient enantioselection in the reaction with allylic substrates having the *Z*-configuration.

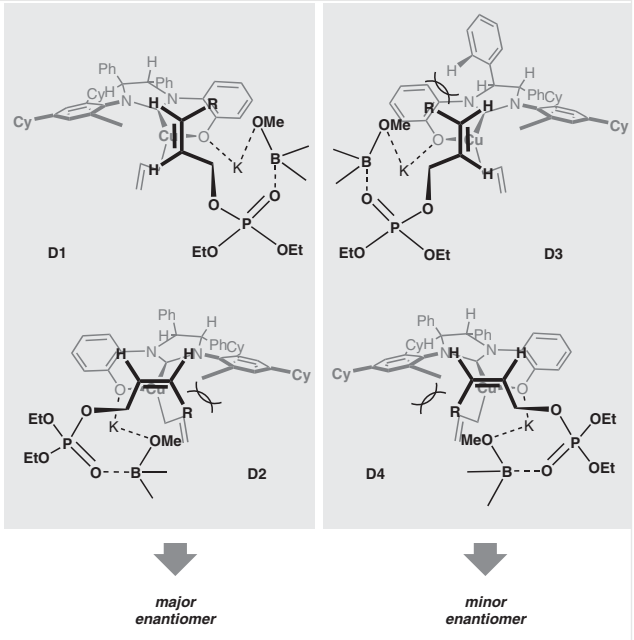


Figure 2 Models for enantioselection with (*Z*)-**2**

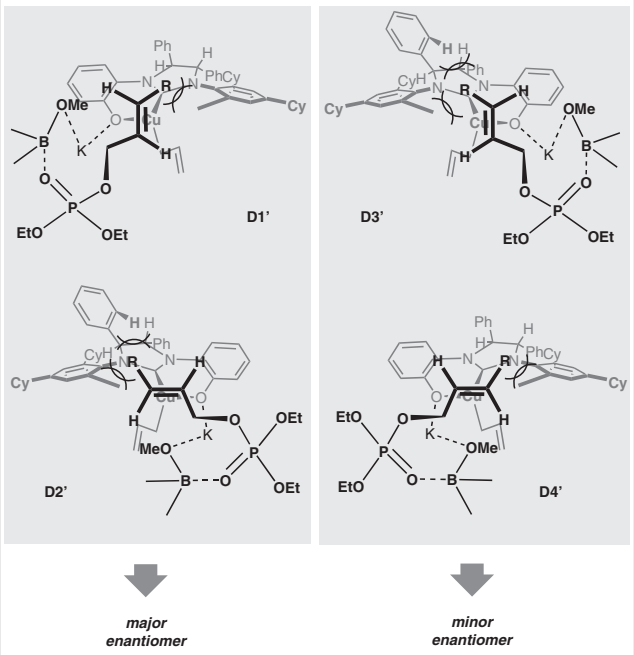


Figure 3 Models for enantioselection with (*E*)-**2**

In conclusion, a versatile method has been developed for Cu-catalyzed enantioselective allyl–allyl coupling between allylboronates and acyclic and cyclic (*Z*)-allylic phosphates to form various chiral 1,5-diene derivatives. Catalysis of a copper(I) complex with a new phenol–NHC chiral ligand enabled the reaction, demonstrating the utility of this class of chiral ligands for enantioselective copper catalysis with organoboron compounds.[12] This Cu-catalyzed protocol provides efficient access to functionalized, enantioenriched chiral 1,5-dienes with a stereogenic carbon center at the allylic/homoallylic position. 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. A functional role for the phenolic hydroxy group in the chiral NHC ligand was suggested by the results.

NMR spectra were recorded on a JEOL ECX-400 instrument, operating at 400 MHz for ^{1}H NMR, 100.5 MHz for ^{13}C NMR, and 128 MHz for ^{11}B NMR acquisitions. Chemical shift values for ^{1}H and ^{13}C NMR data are referenced to TMS and the residual solvent resonances, respectively. Chemical shifts (δ) are reported in ppm. Mass spectra were obtained with a Thermo Fisher Scientific Exactive, JEOL JMS-T100LP, or JEOL JMS-700TZ mass spectrometer at the Instrumental Analysis Division, Global Facility Center, Creative Research Institution, Hokkaido University. HPLC analyses were conducted on an HITACHI ELITE LaChrom system with an HITACHI L-2455 diode array detector or an HITACHI Chromaster system with an HITACHI 5430 diode array detector. Optical rotations were measured on a JASCO P-2200 polarimeter. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck silica gel 60 F_{254}. Silica gel (Kanto Chemical Co., silica gel 60 N, spherical, neutral) was used for column chromatography. IR spectra were measured with a Perkin-Elmer Spectrum One spectrometer. Melting points were measured on a Yanaco MP-500D apparatus. Gel permeation chromatography (GPC) was performed with an LC-908 system (Japan Analytical Industry Ltd., two in-line JAIGEL-2H columns, $CHCl_3$, 3.5 mL/min, UV and RI detectors).All reactions were carried out under nitrogen or argon atmosphere. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. CuCl and KOMe were purchased from Aldrich Chemical Co., stored under nitrogen, and used as received. THF was purchased from Kanto Chemical Co. and stored under argon. 2-Allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1a**) was obtained from commercial suppliers. Allylboronate **1g** was prepared according to the reported procedure.[22] The synthesis of allylboronates **1b–f**, allylic phosphates **2a–r**, **2t–v**, **2a′**, and NHC ligands **L1–7** has been reported previously.[8,12a] (*E*)-**4aa** is known in the literature.[3f]

(*S*,*Z*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-penten-1-yl Diethyl Phosphate [(*S*)-2s]

(*S*)-3-Butyn-2-ol (99% ee) (1.2 mL, 15 mmol) and imidazole (2.0 g, 30 mmol) were dissolved in DCM (30 mL) at 0 °C. Then, TBSCl (3.4 g, 22 mmol) was added to the mixture, and the solution was stirred at rt for 8 h. The reaction was quenched with H_2O and the mixture was extracted with DCM (3 × 15 mL). The combined organic layer was dried over $MgSO_4$. Then, the drying agent was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (0–5% EtOAc/hexane) to give the TBS-protected alcohol derivative (2.6 g, 14 mmol) in 96% yield.

n-BuLi in hexane (9.6 mL, 15.8 mmol) was dropped into a solution of the TBS-protected alcohol (2.6 g, 14 mmol) in Et_2O (29 mL) at –78 °C. The reaction mixture was stirred for 30 min before formaldehyde (877 mg, 29.2 mmol) was added to the mixture. The reaction vessel was removed from the cooling bath. After 12 h of stirring at rt, the reaction was quenched with H_2O. The mixture was diluted with Et_2O and the organic layer was separated. The aqueous phase was extracted with Et_2O (2 × 15 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash chromatography on silica gel (0–10% EtOAc/hexane) afforded the corresponding propargyl alcohol (2.3 g, 10 mmol) in 73% yield.

A solution of the propargyl alcohol (1.1 g, 5 mmol) in hexane (4.3 mL) and acetone (790 µL) was added to a mixture of Pd/$CaCO_3$ (40.0 mg) and quinoline (397 µL, 3.6 mmol), and then the reaction mixture was filled with hydrogen gas. After confirmation of reaction completion by ^{1}H NMR spectroscopy, the Pd/$CaCO_3$ was removed by filtration, and the resulting solution was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (0–10% EtOAc/hexane) to give (*S*,*Z*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-penten-1-ol (874 mg, 4.0 mmol) in 80% yield.

To a solution of (*S*,*Z*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-penten-1-ol (874 mg, 4.0 mmol) in pyridine (6.1 mL), $(EtO)_2P(O)Cl$ (697 µL, 4.8 mmol) and DMAP (24 mg, 0.2 mmol) were sequentially added at 0 °C. After being stirred at rt for 3 h, the reaction mixture was diluted with EtOAc (20 mL) and was treated with H_2O (2 mL). The resulting mixture was washed with saturated aq $CuSO_4$ (3 × 10 mL) and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10–45% EtOAc/hexane) to provide **2s** (1.3 g, 3.8 mmol) in 94% yield. The ee value of (*S*)-**2s** (99% ee) was determined by chiral HPLC analysis of the *p*-methoxybenzoate derivative of (*S*,*Z*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-penten-1-ol [CHIRALCEL® OD-3 column, 4.6 × 250 mm, Daicel Chemical Industries, hexane/2-propanol 99:1, 0.5 mL/min, 40 °C, 220 nm UV detector; t_R = 13.7 (*R*-isomer), 17.7 min (*S*-isomer) min].

Colorless oil; $[\alpha]_D^{25}$ +150 (*c* 1.17, $CHCl_3$); 99% ee.

IR (neat): 667, 775, 830, 975, 1026, 1254, 1369, 1393, 1473, 2858, 2930, 2957 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.06 (s, 3 H), 0.89 (s, 9 H), 1.20 (d, *J* = 6.4 Hz, 3 H), 1.34 (t, *J* = 7.2 Hz, 6 H), 4.11 (quintet, *J* = 7.2 Hz, 4 H), 4.55–4.69 (m, 3 H), 5.48 (dt, *J* = 11.2, 6.0 Hz, 1 H), 5.64 (dd, *J* = 11.2, 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8, –4.6, 16.1 (d, *J* = 6.7 Hz), 18.1, 24.6, 25.7, 63.0 (d, *J* = 4.8 Hz), 63.7 (d, *J* = 5.7 Hz), 65.1, 122.3 (d, *J* = 6.6 Hz), 139.2.

HRMS–ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{33}O_5NaPSi$: 375.17271; found: 375.17227.

Copper-Catalyzed Enantioselective Allyl–Allyl Coupling; Typical Procedure

The reaction in Table 4, entry 1 is representative. CuCl (1.5 mg, 0.015 mmol), **L5**·HBF_4 (9.8 mg, 0.015 mmol), and KOMe (12.6 mg, 0.18 mmol) were placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon®-coated silicon rubber septum, and then the vial was evacuated and filled with argon. THF (0.6 mL) was added to the vial, and then the mixture was stirred at rt for 30 min. Next, 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1a**; 45.3 µL, 0.24 mmol) was added. Finally, allylic phosphate **2b** (42.6 mg, 0.15 mmol) was added at –50 °C. After 48 h stirring at –50 °C, the reaction was

quenched with saturated aq NH_4Cl and the mixture was extracted with Et_2O (3 × 1 mL). The combined organic layer was dried over $MgSO_4$. Then, the drying agent was removed by filtration, and the resulting solution was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane) to give **3ab** (15.9 mg, 0.09 mmol) in 62% yield.

Characterization Data for Allyl–Allyl Coupling Products

Full details for compounds **3aa–am**, **3ap–ar**, **3ba–ea**, **3ft**, **3au**, and **3av** can be found in our previous report.[8]

(*R*)-(3-Vinyl-5-hexen-1-yl)benzene (3aa)

Product **3aa** was purified by flash chromatography on silica gel (hexane) [178.9 mg, 0.96 mmol, 80% isolated yield from (*Z*)-**2a**].

(*S*)-(2-Vinyl-4-penten-1-yl)benzene (3ab)

Product **3ab** was purified by flash chromatography on silica gel (hexane) (15.9 mg, 0.09 mmol, 62% isolated yield from **2b**).

(*S*)-5-(2-Vinyl-4-penten-1-yl)benzo[*d*][1,3]dioxole (3ac)

Product **3ac** was purified by flash chromatography on silica gel (5% Et_2O/hexane) (31.5 mg, 0.14 mmol, 97% isolated yield from **2c**).

(*R*)-4-Vinyl-1-dodecene (3ad)

Product **3ad** was purified by flash chromatography on silica gel (hexane) (24.7 mg, 0.12 mmol, 85% isolated yield from **2d**).

(*R*)-Hexa-1,5-dien-3-ylcyclohexane (3ae)

Product **3ae** was purified by flash chromatography on silica gel (pentane) (14.6 mg, 0.09 mmol, 59% isolated yield from **2e**).

(*R*)-2-[(2-Vinyl-4-penten-1-yl)oxy]tetrahydro-2*H*-pyran (3af)

Product **3af** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (24.3 mg, 0.12 mmol, 83% isolated yield from **2f**); d.r. 1:1.

(*R*)-{[(2-Vinyl-4-penten-1-yl)oxy]methyl}benzene (3ag)

Product **3ag** was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) (22.8 mg, 0.11 mmol, 75% isolated yield from **2g**).

(*R*)-*tert*-Butyldimethyl[(2-vinyl-4-penten-1-yl)oxy]silane (3ah)

Product **3ah** was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) (26.6 mg, 0.12 mmol, 78% isolated yield from **2h**).

(*R*)-2-Vinyl-4-penten-1-yl Pivalate (3ai)

Product **3ai** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (20.6 mg, 0.11 mmol, 70% isolated yield from **2i**).

(*R*)-2-Vinyl-4-penten-1-yl 4-Methoxybenzoate (3aj)

Product **3aj** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (31.2 mg, 0.13 mmol, 85% isolated yield from **2j**).

(*R*)-2-Vinyl-4-penten-1-yl 4-(Trifluoromethyl)benzoate (3ak)

Product **3ak** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (25.9 mg, 0.09 mmol, 61% isolated yield from **2k**).

(*R*)-2-Vinyl-4-penten-1-yl 4-Bromobenzoate (3al)

Product **3al** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (28.8 mg, 0.10 mmol, 65% isolated yield from **2l**).

(*R*)-2-Vinyl-4-penten-1-yl 4-(Dimethylamino)benzoate (3am)

Product **3am** was purified by flash chromatography on silica gel (0–5% EtOAc/hexane) (34.0 mg, 0.13 mmol, 87% isolated yield from **2m**).

(*R*)-1-Benzyl 4-(2-Vinyl-4-penten-1-yl) Piperidine-1,4-dicarboxylate (3ap)

Product **3ap** was purified by flash chromatography on silica gel (5–10% EtOAc/hexane) (43.0 mg, 0.12 mmol, 80% isolated yield from **2p**).

(*R*)-*tert*-Butyldimethyl[(4-vinyl-6-hepten-1-yl)oxy]silane (3aq)

Product **3aq** was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) (29.8 mg, 0.12 mmol, 78% isolated yield from **2q**).

(*R*)-4-Vinyl-6-hepten-1-yl 4-Methylbenzenesulfonate (3ar)

Product **3ar** was purified by flash chromatography on silica gel (0–5% EtOAc/hexane) (38.7 mg, 0.13 mmol, 88% isolated yield from **2r**).

tert-Butyldimethyl{[(2*S*,3*S*)-3-vinyl-5-hexen-2-yl]oxy}silane (3as)

Product **3as** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) [22.2 mg, 0.09 mmol, 51% isolated yield from (*S*)-**2s**]. The absolute configuration of **3as** was assigned by consideration of the stereochemical pathway.

Colorless oil; $[\alpha]_D^{25}$ +34 (*c* 0.37, $CHCl_3$); d.r. 90:10 (determined by ^1H NMR analysis of the crude product).

IR (neat): 664, 772, 830, 910, 994, 1072, 1254, 1361, 1374, 1463, 1472, 1641, 2858, 2887, 2930, 2957, 3078 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.89 (s, 9 H), 1.08 (d, *J* = 6.4 Hz, 3 H), 1.98–2.12 (m, 2 H), 2.34 (m, 1 H), 3.70 (quintet, *J* = 6.4 Hz, 1 H), 4.95–5.08 (m, 4 H), 5.59–5.88 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8, –4.3, 17.9, 20.8, 25.7, 34.5, 51.7, 70.5, 115.2, 115.8, 137.4, 139.1.

HRMS–APCI: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{29}OSi$: 241.19822; found: 241.19826.

(*R*)-(5-Methyl-3-vinyl-5-hexen-1-yl)benzene (3ba)

Product **3ba** was purified by flash chromatography on silica gel (hexane) (23.1 mg, 0.12 mmol, 77% isolated yield from (*Z*)-**2a**).

(*R*)-(5-Methylene-3-vinylheptyl)benzene (3ca)

Product **3ca** was purified by flash chromatography on silica gel (hexane) (16.1 mg, 0.07 mmol, 50% isolated yield from (*Z*)-**2a**).

(*R*)-(5-Methylene-3-vinylundecyl)benzene (3da)

Product **3da** was purified by flash chromatography on silica gel (hexane) (35.3 mg, 0.13 mmol, 87% isolated yield from (*Z*)-**2a**).

(*R*)-(2-Methylene-4-vinylhexane-1,6-diyl)dibenzene (3ea)

Product **3ea** was purified by flash chromatography on silica gel (0–1% Et_2O/hexane) (24.7 mg, 0.08 mmol, 59% isolated yield from (*Z*)-**2a**).

(*R*)-(4-Methyl-1,5-hexadien-2-yl)benzene (3ft)

Product **3ft** was purified by flash chromatography on silica gel (hexane) (23.0 mg, 0.13 mmol, 89% isolated yield from **2t**). The isolated branched product **3ft** was contaminated with a trace amount of the linear product.

(1*R*,2*R*)-2-Allyl-3-cyclopenten-1-yl Diethyl Phosphate (3au)

Product **3au** was purified by flash chromatography on silica gel (20–50% EtOAc/hexane) (25.1 mg, 0.10 mmol, 64% isolated yield from **2u**).

(1*R*,2*R*)-2-Allyl-3-cyclohexen-1-yl Diethyl Phosphate (3av)

Product **3av** was purified by flash chromatography on silica gel (20–50% EtOAc/hexane) (21.3 mg, 0.08 mmol, 52% isolated yield from **2v**).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591548.

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(18) The linear α-substitution product was the (*E*)-isomer.
(19) Data for Schemes 4 and 5 are taken from ref. 8.
(20) 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 Nakamura's mechanism, in which the (γ-σ-enyl)copper(III) species is not in equilibrium with the corresponding (α-σ-enyl)copper(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 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 copper 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, making the allylic 1,3-copper migration in the allylcopper(III) complex more feasible. See: (a) Yoshikai, N.; Zhang, S.-L.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 12862. For the effect of a σ-donor ligand, see: (b) Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 6287.

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