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Copper-Catalyzed Enantioselective Allylic Alkylation of Terminal Alkyne Pronucleophiles

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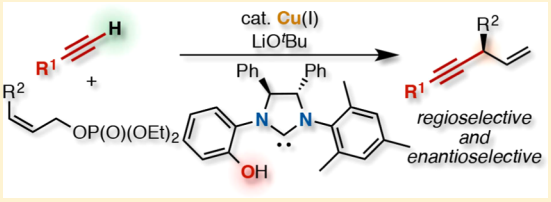
Supporting Information

ABSTRACT: The copper-catalyzed enantioselective allylic alkylation of terminal alkynes with primary allylic phosphates was developed by the use of a new chiral N-heterocyclic carbene ligand bearing a phenolic hydroxy group at the *ortho* position of one of the two *N*-aryl groups. This reaction occurred with excellent γ-branch regioselectivity and high enantioselectivity, forming a controlled stereogenic center at the allylic/propargylic position. Various terminal alkynes, including silyl, aliphatic, and aromatic alkynes, could be used directly without premetalation of the C(sp)−H bond. On the basis of the results of experiments using an isomeric secondary allylic phosphate, which gave a branched product through an α-selective substitution reaction with retention of configuration, a reaction pathway involving 1,3-allylic migration of Cu in a ([σ + π]-allyl)copper(III) species is proposed.



INTRODUCTION

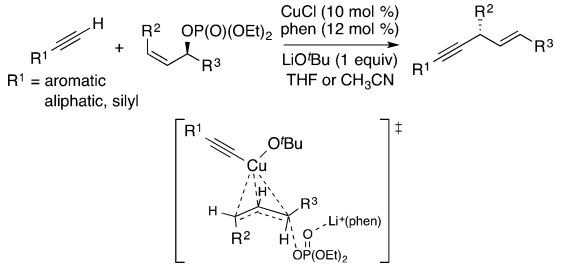
Catalytic enantioselective allylic alkylation of alkynyl nucleophiles is a powerful strategy for asymmetric organic synthesis. Readily available precursors are easily transformed into chiral 1,4-enynes (skipped enynes), which are versatile synthetic intermediates with two different handles for further transformations connected to the stereogenic carbon center.[1−5] To date, this has been achieved by using metal acetylide reagents. Hoveyda[2a,b] and Carreira[2c] used alkynylaluminum and alkynylboron reagents with copper and iridium catalyst systems, respectively. However, the strongly basic and nucleophilic natures of the metalating reagents and the metal acetylides reduce the functional group compatibility of these methods. Accordingly, a catalytic enantioselective allylic alkylation using terminal alkynes directly as pronucleophile substrates is highly desirable, due to its potential for the convergent synthesis of complex molecules.[6]

Here, we report copper-catalyzed enantioselective allylic alkylation using terminal alkynes and primary allylic phosphates as the substrate couple in the presence of a stoichiometric LiO^{t}Bu base.[7] This reaction occurred with excellent γ-branch regioselectivity and high enantioselectivity, forming a controlled stereogenic center at the allylic/propargylic position. This was facilitated by the catalysis of a copper(I) complex with a chiral N-heterocyclic carbene (NHC) ligand bearing a phenolic hydroxy group at the *ortho* position of one of the two *N*-aryl groups. Various terminal alkynes, including silyl, aliphatic, and aromatic alkynes, could be used directly without premetalation of the C(sp)−H bond. Thus, base-sensitive functional groups such as primary alkyl tosylate and *p*-nitrobenzoate were compatible with this enantioselective reaction.

RESULTS AND DISCUSSION

Optimization of Copper-Catalyzed Enantioselective Allylic Alkylations of Terminal Alkynes. Earlier, we reported that allylic alkylation of terminal alkynes with enantioenriched chiral secondary (*Z*)-allylic phosphates proceeded with excellent S_N2'-type regioselectivity and 1,3-*anti* stereospecificity under the influence of a catalytic amount of Cu(I) salt/1,10-phenanthroline and a stoichiometric LiO^{t}Bu base (Scheme 1).[8] The use of LiO^{t}Bu was important for promotion of the reaction. Therefore, we inferred that a Li^+ ion activated the phosphate leaving group as a Lewis acid and that the ancillary effect of 1,10-phenanthroline was due to binding to the Li^+ ion.

Scheme 1. Previous Work[8]



With this knowledge, we initiated a program to develop catalytic enantioselective allylic alkylations using terminal alkynes and achiral primary allylic phosphates as the substrate couple. Initial screening of leaving groups was conducted for the reaction of (*Z*)-5-phenyl-2-pentenol derivatives **2** with

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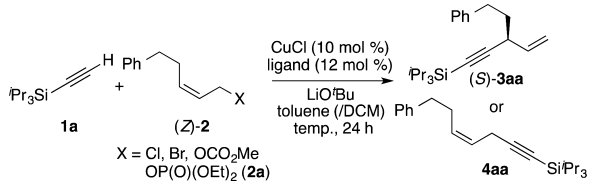
Table 1. Copper-Catalyzed Enantioselective Allylic Alkylations of Terminal Alkyne 1a with (*Z*)-Allylic Substrate 2[a]



entry	leaving group X	ligand	amt of LiO^{t}Bu (equiv)	temp (°C)	yield (%)[b]	b/l[c] (3aa:4aa)	ee (%)[d]
1	Cl	none	1.3	40	0		
2	Br	none	1.3	40	0		
3	OCO$_2$Me	none	1.3	40	0		
4	OP(O)(OEt)$_2$	none	1.3	40	53	17:83	
5	OP(O)(OEt)$_2$	Phen	1.3	40	68	18:82	
6	OP(O)(OEt)$_2$	PPh$_3$	1.3	40	22	18:82	
7	OP(O)(OEt)$_2$	DPPE	1.3	40	41	20:80	
8	OP(O)(OEt)$_2$	SIMes	1.3	40	48	96:4	
9	OP(O)(OEt)$_2$	IMes	1.3	40	16	>99:1	
10	OP(O)(OEt)$_2$	**L1**	1.3	40	64	91:9	43
11	OP(O)(OEt)$_2$	**L2**	1.3	40	98	83:17	53
12[e,f]	OP(O)(OEt)$_2$	**L2**	2.6	−50	0		
13	OP(O)(OEt)$_2$	**L3**	1.3	40	88	87:13	7
14	OP(O)(OEt)$_2$	**L4**	1.3	40	96	>99:1	65
15[e]	OP(O)(OEt)$_2$	**L4**	1.3	0	99	>99:1	71
16[e]	OP(O)(OEt)$_2$	**L4**	1.3	−20	81	>99:1	75
17[e]	OP(O)(OEt)$_2$	**L4**	1.3	−50	40	>99:1	85
18[e]	OP(O)(OEt)$_2$	**L4**	2.6	−50	64	>99:1	85
19[e,f]	OP(O)(OEt)$_2$	**L4**	2.6	−50	66	>99:1	92
20	OP(O)(OEt)$_2$	**L5**	1.3	40	94	>99:1	62
21	OP(O)(OEt)$_2$	**L6**	1.3	40	92	>99:1	28
22	OP(O)(OEt)$_2$	**L7**	1.3	40	93	>99:1	38

[a]The reaction was carried out with **1a** (0.18 mmol), **2** (0.15 mmol), CuCl (10 mol %), ligand (12 mol %), and LiOtBu (1.3 or 2.6 equiv to (*Z*)-**2a**) in toluene (0.6 mL) for 24 h unless otherwise noted. [b]The yield of isolated product. [c]The ratio was determined by ^{1}H NMR analysis of the crude product. [d]The enantiomeric excess was determined by HPLC analysis. [e]The reaction was carried out for 48 h. [f]The reaction solvent was toluene/DCM 4/1.

triisopropylsilylacetylene (**1a**) in the presence of CuCl (10 mol %) and LiO^{t}Bu (1.3 equiv) in toluene at 40 °C, and we confirmed that a phosphate was the only effective leaving group among those examined (Table 1, entries 1−4). In fact, the reaction between **1a** and (*Z*)-allylic phosphate **2a** afforded the linear, achiral product **4aa** with (*Z*)-alkene geometry as the major isomer (branched/linear (b/l) 17:83) (Table 1, entry 4).[9]

Next, various achiral ligands were screened for the selective formation of the racemic, branched product (**3aa**) in the reaction between **1a** and (*Z*)-**2a** in the presence of CuCl (10 mol %) and LiO^{t}Bu in toluene at 40 °C (Table 1, entries 5−9).[9] Even with 1,10-phenanthroline (Phen), which gave excellent S_N2'-type selectivity in the previously reported reaction with secondary allylic phosphates,[8] the linear product **4aa** was obtained as the major isomer (entry 5). Monodentate and bidentate phosphine ligands such as Ph$_3$P and 1,2-diphenylphosphinoethane (DPPE) showed similar regioselectivities with less efficient substrate conversions (entries 6 and 7). However, a copper N-heterocyclic carbene (SIMes; Figure 1) complex prepared in situ from 1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride (SIMes·HCl), CuCl, and LiO^{t}Bu showed favorable branch selectivity (b/l 96:4) with moderate chemical yield (entry 8).[10] The use of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl; Figure 1) resulted in exclusive branch selectivity (b/l > 99:1), but the yield was low (16%) (entry 9).

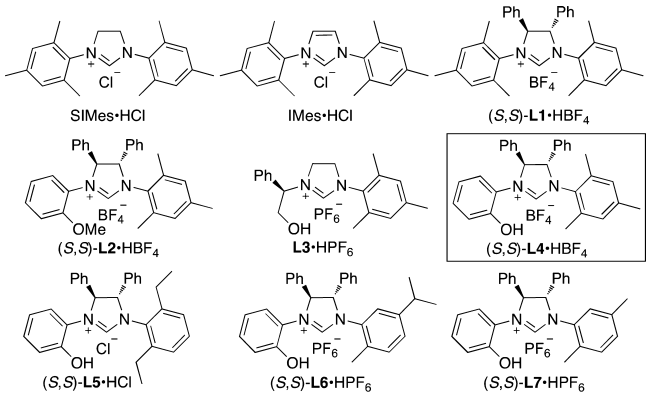


Figure 1. Achiral and chiral NHC ligands (shown in forms of HX salts). The HX salts of **L2**−**L7** were newly synthesized in this study.

On the basis of these results, we investigated various chiral NHC ligands (**L1**−**L7**; Figure 1).[9] The results obtained under the conditions used for the screening of the achiral ligands (toluene, 40 °C, 24 h) are shown in Table 1, entries 10, 11, 13, 14, and 20−22.[9−11] The ring-saturated C_2-symmetric NHC ligand (*S*,*S*)-**L1**,[12] which has two stereogenic carbon centers in the imidazolidine ring with two mesityl groups at both nitrogen atoms, produced the branched 1,4-enyne isomer (*S*)-**3aa** with moderate enantioselectivity (43% ee) and 91% branch regioselectivity (entry 10).[13] A similar chiral NHC ligand,

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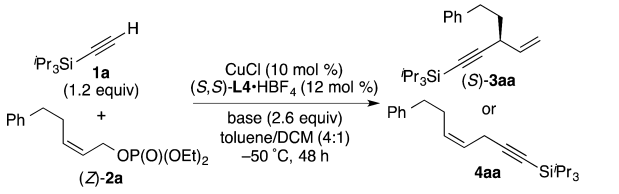
(*S*,*S*)-**L2**, bearing a 2-methoxyphenyl group instead of one of the mesityl groups in **L1** gave better chemical yield and enantioselectivity (53% ee) but decreased branch selectivity (b/l 83:17) (entry 11). Next, we investigated the effect of incorporating the function of an alkoxide base within the chiral NHC ligand. The *N*-hydroxyalkyl NHC ligand **L3**,[14] having a stereogenic center only in the *N*-alkyl side arm, gave nearly racemic **3aa** (entry 13). On the other hand, the phenol type ligand (*S*,*S*)-**L4** with a diphenylethylenediamine-derived NHC core imparted an enantioselectivity (65% ee) better than those of the nonhydroxylated NHC ligands (*S*,*S*)-**L1** and **L2** with exceptional branch selectivity (b/l > 99:1) and excellent yield (96%) (entry 14). This result suggests a functional role of the phenolic hydroxy group in (*S*,*S*)-**L4**. A change of the mesityl group of (*S*,*S*)-**L4** to other aromatic groups ((*S*,*S*)-**L5**−**L7**) did not lead to an improvement in enantioselectivity; however, the excellent branch regioselectivity was maintained (entries 20−22).

The enantioselectivity with the Cu-(*S*,*S*)-**L4** catalyst was improved to 85% ee by lowering the reaction temperature to −50 °C with a reduction of the yield (40%) (Table 1, entries 15−17).[9] A higher yield (64%) was obtained with an increased amount of Li*O*^{t}Bu, with the enantioselectivity unchanged (entry 18). Thereafter, we found that the mixed solvent system toluene/DCM (4/1) gave an enantioselectivity as high as 92% ee (entry 19). In contrast to the phenol-containing ligand (*S*,*S*)-**L4**, the anisol-substituted ligand (*S*,*S*)-**L2** induced no reaction at −50 °C (entry 12). Thus, (*S*,*S*)-**L4** produced much more active catalyst than (*S*,*S*)-**L2**. This result strongly suggests cooperative participation of an ionized OH group in the catalysis.

The nature of the base had a strong impact on the yield, branch regioselectivity, and enantioselection, as in the case for the copper-catalyzed alkynylation of secondary allylic phosphates.[8,9] For example, replacing Li*O*^{t}Bu in the reaction of **1a** and (*Z*)-**2a** with Na*O*^{t}Bu under thus far optimized conditions (Table 1, entry 19 and Table 2, entry 1) caused a significant decrease in chemical yield (53%), branch selectivity (b/l 88:12), and enantioselectivity (73% ee) (Table 2, entry 2). No reaction occurred with K*O*^{t}Bu (entry 3). The combined use of K*O*^{t}Bu and LiCl (1/1) resulted in no reaction (entry 4). When Li*O*^{t}Bu was changed to the sterically less demanding base LiOEt, the chemical yield was low and enantioselectivity decreased to 74% ee, but the excellent branch regioselectivity was retained (entry 5). The even smaller alkoxide base LiOMe induced no reaction (entry 6). The use of Li_2CO_3 resulted in no reaction (entry 7).

Table 2. Base Effect[a]



entry	base	yield (%)[b]	b/l[c] (**3aa**:**4aa**)	ee (%)[d]
1	Li*O*^{t}Bu (Table 1, entry 19)	66	>99:1	92
2	Na*O*^{t}Bu	53	88:12	73
3	K*O*^{t}Bu	0		
4	K*O*^{t}Bu/LiCl (1/1)	0		
5	LiOEt	20	>99:1	74
6	LiOMe	0		
7	Li_2CO_3	0		

[a]The reaction was carried out with **1a** (0.18 mmol), (*Z*)-**2a** (0.15 mmol), CuCl (10 mol %), (*S*,*S*)-**L4**·HBF_4 (12 mol %), and base (0.39 mmol) in toluene/DCM (4/1, 0.6 mL) for 48 h. [b]The yield of isolated product. [c]The ratio was determined by ^{1}H NMR analysis of the crude product. [d]The enantiomeric excess was determined by HPLC analysis.

Substrate Scopes. Various allylic phosphates with different steric demands at the γ position were then subjected to the allylic alkylation of **1a** with the Cu-(*S*,*S*)-**L4** catalyst system in toluene/DCM (4/1) at −50 or −30 °C (Table 3).[9,13] The allylic phosphates with methyl, ethyl, or octyl groups at the position γ to the leaving group were converted to the corresponding products with excellent branch selectivities (b/l > 99:1) and with high enantioselectivities (entries 1−3). A sterically more demanding γ substituent such as a cyclohexyl group was also tolerated, with a high level of enantioselectivity (91% ee) being retained (entry 4).

Due to the mildness of the reaction conditions, various functional groups were tolerated (Table 3, entries 5−14). For example, allylic phosphates (**2**) bearing silyl ether (**2f**), pivalate (**2g**), THP ether (**2h**), and *p*-toluenesulfonate (**2i**) groups as the aliphatic γ substituent reacted at −30 °C to afford the corresponding enyne products in good yields with high enantioselectivities (90−95% ees) (entries 5−8). Notably, even the base-sensitive *p*-nitrobenzoate moiety survived under the reaction conditions (entry 9). Bromo, cyano, ketone, and dimethylamino substituents in the aromatic ring of the benzoate groups were also tolerated (entries 10−13). A carbamate group was compatible with this enantioselective reaction (entry 14).

The effects of the structure of the alkyne substrate on the reactivity, regioselectivity, and enantioselectivity were examined in the reaction with (*Z*)-**2a** (Table 4).[9,13] The silylacetylenes **1b**−**d**, with silyl groups other than the triisopropylsilyl group, also served as substrates to produce the corresponding 1,4-enynes in good to high yields, with a tendency toward increased regioselectivities and enantioselectivities with the increasing steric demands of the silyl substituents (entries 1−3).

Various aliphatic alkynes **1e**−**g**) with different degrees and patterns of branching reacted with (*Z*)-**2a** with excellent branch selectivities (b/l > 99:1) and with reasonably high enantioselectivities, although the enantioselectivity in the reaction of the linear aliphatic alkyne **1e** was relatively low (73% ee) (Table 4, entries 4−7).[9,13] The diastereoselective reactions with *O*-protected chiral propargylic alcohols (*S*)-**1h** and (*S*)-**1i** produced controlled stereogenic centers at both the propargylic positions with diastereocontrols of 91:9 and 89:11, respectively (entries 8, 9, and 11).[15] On the other hand, the reaction with the *R* isomer of **1h** gave a slightly decreased diastereoselectivity (87:13), showing a minor match/mismatch effect (entry 10). The use of tertiary propargylic alcohol **1j** also gave a reasonably high enantioselectivitiy (entry 12). The *N*,*N*-dibenzylpropargylamine derivative (**1k**) reacted with high enantioselectivity (entry 13). Phenylacetylene (**1l**) reacted with an enantioselectivity (65% ee) lower than those for the aliphatic alkynes (entry 14).[15] The 1,3-enyne derivative **1m** afforded dienyne **3ma** with moderate enantiocontrol (70% ee) (entry 15).[15]

Effect of Alkene Geometry. The alkene geometry of the substrate is important for enantioselectivity and/or reactivity. The reaction of (*E*)-**2a** under the optimized conditions (the conditions for Table 1, entry 19) afforded (*R*)-**3aa**, the antipode of the product derived from (*Z*)-**2a**, with exceptional

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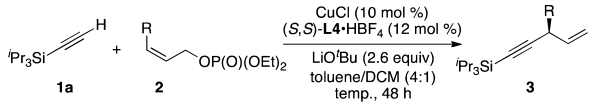
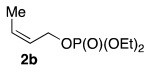
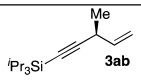
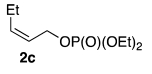
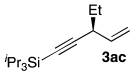
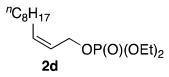
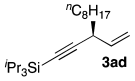
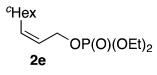
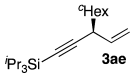
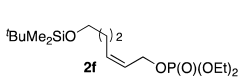
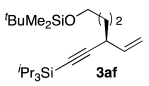
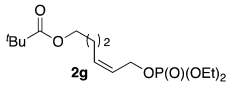
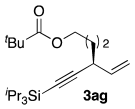
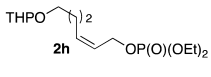
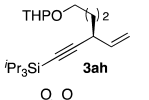
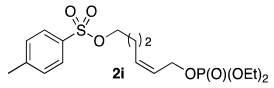
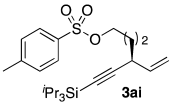
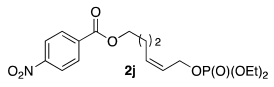
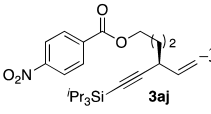
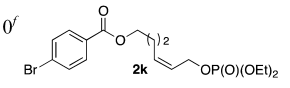
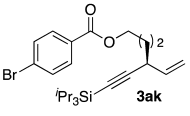
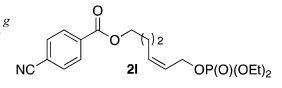
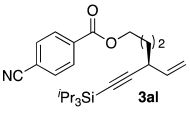
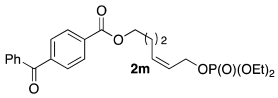
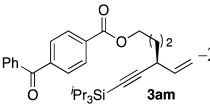
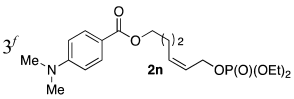
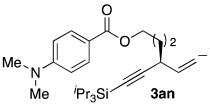
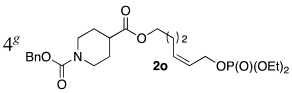
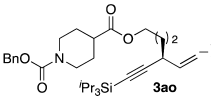
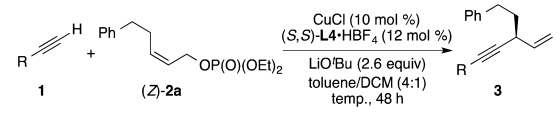
Table 3. Scope of Enantioselective Allylic Alkylation of 1a[a]

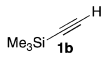
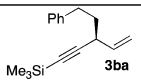
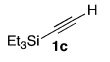
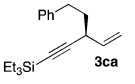
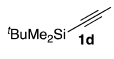
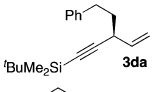
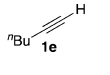
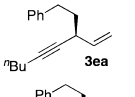
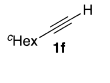
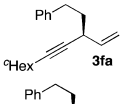


entry	phosphate	product	temp (°C)	yield (%)[b,c]	ee (%)[d]
1	 2b	 3ab	–50	55	91
2	 2c	 3ac	–30	75	90
3	 2d	 3ad	–50	61	92
4	 2e	 3ae	–50	70	91
5	 2f	 3af	–30	73	90
6	 2g	 3ag	–30	76	90
7[e]	 2h	 3ah	–30	75	90
8	 2i	 3ai	–30	65	95
9	 2j	 3aj	–30	61	93
10[f]	 2k	 3ak	–30	76	92
11[g]	 2l	 3al	–10	79	92
12	 2m	 3am	–20	79	90
13[f]	 2n	 3an	–10	90	88
14[g]	 2o	 3ao	–10	73	90

[a]The reaction was carried out with **1a** (0.18 mmol), **2** (0.15 mmol), CuCl (10 mol %), (*S,S*)-**L4**·HBF_4 (12 mol %), and LiO^tBu (0.39 mmol) in toluene/DCM (4/1, 0.6 mL) for 48 h. [b]The yield of isolated product. [c]Constitutional isomer ratio b/l > 99:1 (determined by ^1H NMR analysis of the crude product). [d]The enantiomeric excess was determined by HPLC analysis. [e]Diastereomeric ratio 1:1. [f]Constitutional isomer ratio b/l 90:10. [g]LiO^tBu (0.19 mmol) was used.

Table 4. Enantioselective Allylic Alkylation of Various Alkynes 1 with 2a[a]



entry	alkyne	product	temp (°C)	yield (%)[b]	b/l[c]	ee (%)[d]
1	 1b	 3ba	–30	73	92:8	74
2	 1c	 3ca	–30	85	94:6	83
3	 1d	 3da	–30	91	>99:1	84
4	 1e	 3ea	–20	49	>99:1	73
5	 1f	 3fa	–20	56	>99:1	83
6	1g	3ga	–20	65	>99:1	83
7			–40	56	>99:1	85
8	(*S*)-**1h**, >99% ee	3ha	–20	91	>99:1	91:9[e]
9[f]			–20	60	>99:1	91: 9[e]
10	(*R*)-**1h**, >99% ee	3ha'	–20	88	>99:1	87:13[e]
11	(*S*)-**1i**, >99% ee	3ia	–40	90	>99:1	89:11[e]
12	1j	3ja	–30	84	>99:1	81
13	1k	3ka	–30	88	>99:1	86
14[g]	1l	3la	–40	64	96:4	65
15	1m	3ma	–20	85	93:7	70

[a]The reaction was carried out with **1** (0.18 mmol), (*Z*)-**2a** (0.15 mmol), CuCl (10 mol %), (*S,S*)-**L4**·HBF_4 (12 mol %), and LiO^tBu (0.39 mmol) in toluene/DCM (4/1, 0.6 mL) for 48 h. [b]The yield of isolated product. [c]The ratio was determined by ^1H NMR analysis of the crude product. [d]The enantiomeric excess was determined by HPLC analysis. [e]Diastereomeric ratio. [f](S)-**1h** (1.02 mmol) and (*Z*)-**2a** (0.85 mmol) were used. [g]The reaction was in toluene.

branch selectivity (>99:1), but in low product yield (11%) with merely 28% ee (eq 1).[9] The reactions of other *E* substrates resulted in similarly low yields and enantioselectivities (see the Supporting Information), showing that further investigations are required for the reactions of these substrates.

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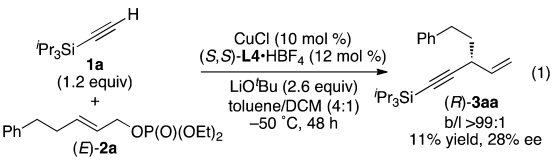
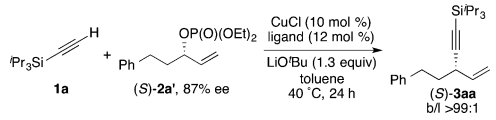


Copper-Catalyzed Allylic Alkynylations with an Enantioenriched Secondary Allylic Phosphate. To see whether or not the branch regioselectivity of the present copper-catalyzed allylic alkylation was due to an S_N2'-type reaction pathway, which is common in most copper-catalyzed/-mediated allylic substitution reactions,[1,16] we conducted comparative experiments with the enantioenriched secondary allylic phosphate (*S*)-**2a**′ (87% ee), a constitutional isomer of **2a**, as a substrate for the reaction with **1a** (Table 5). Contrary to our expectations based on the knowledge on the related copper catalysis, the reaction with the Cu-(*S*,*S*)-**L4** catalyst produced the branched product (*S*)-**3aa** exclusively (b/l > 99:1) (entry 1). The enantiomeric purity of (*S*)-**2a**′ was completely preserved with retention of the stereochemical configuration. Even with (*R*,*R*)-**L4**, the configuration was retained efficiently (entry 2).

Table 5. Copper-Catalyzed Allylic Alkylations of Terminal Alkyne 1a with the Enantioenriched Secondary Allylic Phosphate (*S*)-2a′[a]



entry	ligand	yield (%)[b]	ee (%)[c]
1	(*S*,*S*)-**L4**	87	87
2	(*R*,*R*)-**L4**	86	77

[a]The reaction was carried out with **1a** (0.18 mmol), (*S*)-**2a**′ (0.15 mmol), CuCl (10 mol %), and ligand (12 mol %) in toluene (0.6 mL) at 40 °C for 24 h. [b]The yield of isolated product. [c]The enantiomeric excess was determined by HPLC analysis.

This interesting regiochemical convergence observed in the reactions with isomeric substrates **2a** and (*S*)-**2a**′ suggests strongly that 1,3-allylic migration of Cu in the allylcopper(III) species was involved and that (*S*)-**3aa** was produced from the most stable species.[16] A possible reaction pathway for the α-branch-selective alkynylation of the enantioenriched secondary allylic phosphate **2**′ with Cu-(*S*,*S*)-**L4** that can explain the retention of configuration is illustrated in Figure 2. The chiral NHC ligand coordinates to Cu as an anionic C,O-bidentate ligand. The initial interaction of alkyne **1** to Cu is η^2 coordination to form **A**. Next, **A** recruits LiO^{t}Bu through a C(sp)−H···O hydrogen bond and O···Li$^+$···O ionic interactions to form **B**. Deprotonation−cupration of the C(sp)−H bond affords lithium phenoxo(alkynyl)cuprate **C**. The Li$^+$ ion bridges the anionic acetylide carbon and phenoxide oxygen atoms in **C** (see Proposed Models for Enantiodiscrimination for the importance of the location of the Li$^+$ ion for enantioselection). Next, the secondary allylic phosphate **2**′ binds to Cu (formation of **D**), adopting a conformation avoiding A^{1,3} strain. The copper center attacks the terminal carbon in a *syn*-S_N2' manner with the intramolecular assistance of the Li$^+$ ion as a Lewis acid to activate the phosphate leaving group, resulting in allylic oxidative addition to form the (π-en-σ-yl)copper(III) complex **E1**. In this complex, the σ-bonded sp^3 carbon atom and the η^2-coordinated alkene moiety of the allyl ligand are located at the positions pseudo *trans* and *cis* to the acetylide carbon, respectively. Due to this geometry, this copper(III) complex **E1** may be resistant to reductive elimination to form the linear skipped enyne **4** and undergo 1,3-allylic migration of Cu, leading to the more stable isomer **E2**. Reductive elimination of this complex (**E2**) affords the branched isomer **3** and the copper(I) complex **A**. The observed complete retention of configuration indicates that the π-face inversion of the alkene moiety in the allyl ligand in **E1** is slower than the 1,3-migration−reductive elimination sequence.

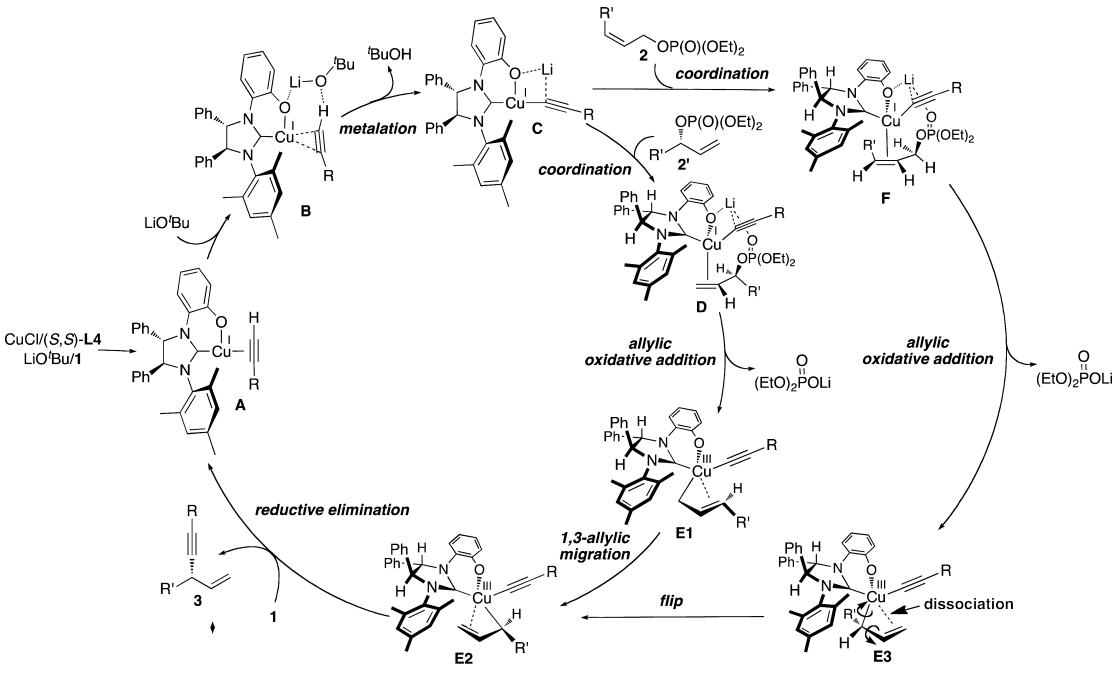


Figure 2. Proposed reaction pathways for allylic alkylations of terminal alkynes **1** catalyzed by the Cu-(*S*,*S*)-**L4** system.

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Proposed Reaction Pathway for the Allylic Alkylation of Terminal Alkynes with Primary Allylic Phosphates. The above discussion on the reaction pathway of the α-selective alkynylation of (*S*)-**2a**′ may provide insight into the mechanism of the enantioselective reaction of the primary allylic phosphates (*Z*)-**2**. A proposed reaction pathway giving the major enantiomer of the skipped enyne **3** is also shown in Figure 2. In this reaction pathway, diastereoselective π coordination of the alkene moiety toward the lithium (alkynyl)(aryloxo)cuprate **C** forms **F**. Li^+-assisted allylic oxidative addition gives a (π-en-σ-yl)copper(III) complex (**E3**) with a secondary sp^3 carbon atom bound to Cu. Due to steric repulsions between the γ substituent R′ and the chiral NHC ligand **L4**, this intermediate is relatively unstable and isomerizes to the more stable isomer **E2** with retention of the configuration at the secondary sp^3 carbon atom. This intermediate (**E2**) is common to the reaction pathway with **2**′. The isomerization is accomplished through a flip of the allyl ligand associated with dissociation of the π coordination of the alkene moiety, probably by way of some isomeric intermediates. The $A^{1,3}$ strain in the allyl ligand may also contribute to the lability of the π-en-σ-yl coordination. Finally, reductive elimination of **E2** gives the major enantiomer of the skipped enyne **3**.

Evaluation of Cu–Ligand Coordination: Effect of the Phenolic Hydroxy Group of L4. The NHC ligands lacking a phenolic hydroxyl group (IMes, **L1**–**3**), except for SIMes, gave reduced regioselectivities in comparison with the phenolic chiral ligand **L4** (Table 1, entries 8–11, 13, and 14). This may be due to the partial dissociation of these monodentate ligands (IMes, **L1**–**3**): NHC-ligated catalytic copper species promote excellent branch selectivity, while NHC-free reaction pathways produce the linear isomer **4aa** preferentially, as is the case with no added ligand shown in Table 1, entry 4 (b/l 17:83). To test this assumption, we investigated the effects of (*S*,*S*)-**L2**/Cu molar ratios on the regio- and enantioselectivities of the reaction between **1a** and (*Z*)-**2a**. As shown in Figure 3, the branch regioselectivity (74–97%) was markedly improved with the enantioselectivity (43–57% ees) nearly unchanged as the (*S*,*S*)-**L2**/copper ratio was increased in the range from 0.6 to 3.6. These results are in accord with the above assumption and thus indicate that C,O-bidentate chelation by the phenolic chiral ligand **L4** allows robust ligand coordination toward catalytic copper species, which is important for constructing a chiral environment favorable for enantioselection.

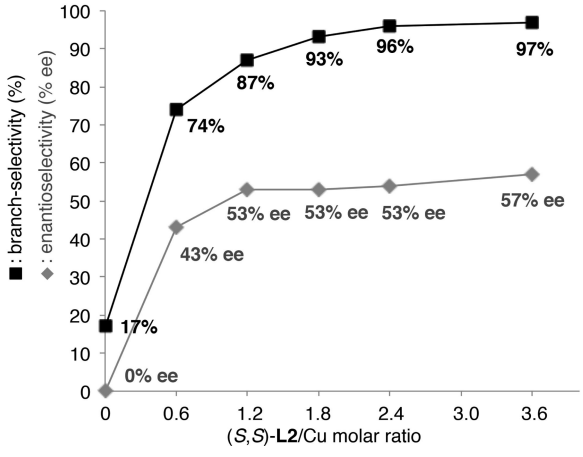

Figure 3. Effects of (*S*,*S*)-**L2**/Cu molar ratios and the regio- and enantioselectivity of the reaction between **1a** (0.18 mmol) and (*Z*)-**2a** (0.15 mmol). Conditions: CuCl, 10 mol %; LiO^tBu; toluene, 0.6 mL; 40 °C; 24 h. All reactions produced the skipped enynes **3aa** + **4aa** in 98% total yield.

Similarly, we investigated the effects of 1,10-phenanthroline/Cu molar ratios on the regioselectivity of the reaction between **1a** and (*Z*)-**2a** (Figure 4). When the 1,10-phenanthroline/Cu molar ratio was increased in the range from 0.6 to 2.4, the low branch regioselectivity (18%) was constant. Although 0.6 and 1.2 equiv of phenanthroline slightly increased the product yield, further loading of this additive caused inhibition of the reaction as a function of the loading. These results suggest that phenanthroline–copper coordination produced inactive species and that 1 molar equiv of phenanthroline favored the copper catalysis. Importantly, this should not be through chelation to the Cu atom but more probably through interaction with the Li^+ ion, because the bidentate coordination of phenanthroline to an (alkoxo)(alkynyl)cuprate produces an 18e complex, which does not accept the coordination of the allylic substrate. This is consistent with the mechanism we proposed previously for the stereospecific reaction between terminal alkynes and chiral secondary allylic phosphates (Scheme 1).[8]

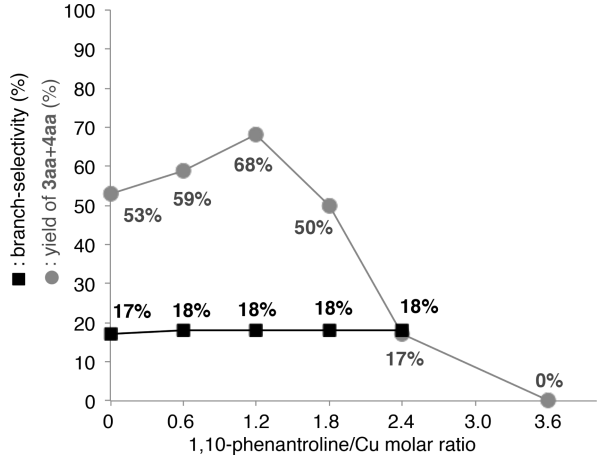

Figure 4. Effects of 1,10-phenanthroline/Cu molar ratios and the regioselectivity of the reaction between **1a** (0.18 mmol) and (*Z*)-**2a** (0.15 mmol). Conditions: CuCl, 10 mol %; LiO^tBu; toluene, 0.6 mL; 40 °C; 24 h.

Proposed Models for Enantiodiscrimination. We propose the enantioselection models depicted in Figure 5 on the basis of the fact that the reaction of the *Z* isomer of **2a** showed enantioselectivity higher than that of the *E* isomer (Table 1, entry 19, vs eq 1). In the π complex **F** (see Figure 2), the copper adopts a tetrahedral coordination geometry and the Li^+ ion bridges the anionic acetylide carbon, phenoxide oxygen, and phosphate leaving group. This well-defined location of the Li^+ ion is important. According to these assumptions, **F1** has less steric strain than **F2**, because the mesityl substituent is proximal to the γ substituent (R′) of **2** in **F2**. These considerations are consistent with the experimental observations that the enantioselectivity is significantly influenced by the steric nature of the nonhydroxylated *N*-aryl group in the phenol type NHC ligands (**L4**–**L7**, Table 1, entries 14 and 20–22). The *ortho*,*ortho* disubstitution in **L4** and **L5** was critical for the high enantioselectivity. The ligands **L6** and **L7**, with 2,5-disubstituted *N*-aryl groups, were much less effective.

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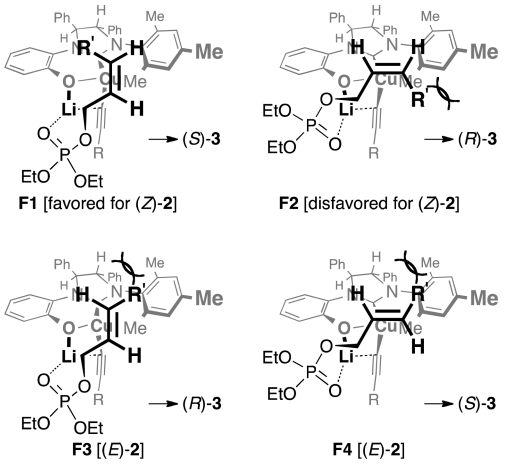

Figure 5. Models for enantiodiscrimination.

In the case of the reaction of (*E*)-**2**, the mesityl substituent causes steric repulsions toward the R′ substituent in both **F3** and **F4**. Thus, the energy difference between these intermediates is smaller than that between **F1** and **F2**. These considerations explain the more efficient enantioselection in the reaction with the allylic substrates with a *Z* configuration.

CONCLUSION

The Cu-catalyzed γ-branch-selective, enantioselective allylic alkylation of terminal alkynes using primary allylic phosphates as electrophiles was developed by the use of a new chiral NHC ligand bearing a phenolic hydroxy group at the *ortho* position of one of the two *N*-aryl groups. This protocol produces enantioenriched chiral skipped enynes with a tertiary stereogenic center at the allylic/propargylic position. Various terminal alkynes, including silyl, aliphatic, and aromatic alkynes, can be used directly without premetalation of the C(sp)−H bond. A reaction pathway involving 1,3-allylic migration of Cu in a ([σ+π]-allyl)copper(III) species was proposed. Mechanistic investigations aided by theoretical calculations are currently ongoing in our laboratory.

EXPERIMENTAL SECTION

Procedure for the Copper-Catalyzed Allylic Alkylation (Table 4, Entry 9). CuCl (8.4 mg, 0.085 mmol), **L4** (53 mg, 0.102 mmol), and LiO^{t}Bu (176 mg, 2.21 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. Toluene (2.7 mL) was placed in the vial, and then the mixture was stirred at room temperature for 5 min. Next, the chiral propargylic alcohol derivative (*S*)-**1h** (230 mg, 1.02 mmol) and CH_2Cl_2 (0.7 mL) were added. Finally, allylic phosphate (*Z*)-**2a** (253 mg, 0.85 mmol) was added at −20 °C. After 48 h of stirring at −20 °C, the reaction mixture was diluted and extracted with diethyl ether (5 mL × 3). The combined organic layers were filtered through a short plug of silica gel with diethyl ether as an eluent. After the volatiles were removed under reduced pressure, flash column chromatography on silica gel (0−3% EtOAc/hexane) gave **3ha** (188 mg, 0.5 mmol) in 60% yield.

ASSOCIATED CONTENT

Supporting Information

Text and figures giving experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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