Asymmetric Catalysis

International Edition: DOI: 10.1002/anie.201600619
German Edition: DOI: 10.1002/ange.201600619

Construction of Quaternary Stereogenic Carbon Centers through Copper-Catalyzed Enantioselective Allylic Alkylation of Azoles

Hirohisa Ohmiya, Heng Zhang, Saori Shibata, Ayumi Harada, and Masaya Sawamura**

Abstract: *Copper-catalyzed enantioselective allylic alkylation of azoles with γ,γ-disubstituted primary allylic phosphates was achieved using a new chiral N-heterocyclic carbene ligand bearing a naphtholic hydroxy group. This reaction occurred with excellent branch regioselectivity and high enantioselectivity, thus forming a controlled all-carbon quaternary stereogenic center at the position α to the heteroaromatic ring.*

Enantioselective construction of quaternary stereogenic centers is an important challenge in modern organic synthesis.[1] More specifically, direct introduction of tertiary alkyl groups onto heteroarene scaffolds through enantioselective catalysis has been actively studied in recent years, but reported examples are limited to alkylation reactions of electron-rich heteroarenes, most studies being focused on C3 alkylation of indoles.[2–5] For instance, Hu and co-workers developed a rhodium/Brønsted acid cocatalyzed tertiary alkylation reaction of indoles and pyrroles based on C(sp^2)−H insertion of rhodium(II) carbenoids derived from α-diazo acetates,[2] and Friedel–Crafts-type indole alkylations with organocatalysts or transition-metal catalysts have been reported by other groups.[3,4] More recently, Sigman and co-workers reported tertiary alkylation of indoles through a palladium-catalyzed enantioselective dehydrogenative Heck reaction with trisubstituted alkenes.[5] In contrast, enantioselective introduction of tertiary alkyl groups through C(sp^2)−H alkylation of electron-deficient heteroarenes, a reaction which should be mechanistically different from that of electron-rich heteroarenes, remains a challenge.[6–8]

We previously reported that copper-catalyzed allylic alkylation of electron-deficient heteroarenes (oxazoles, oxadiazoles, thiazoles, and pyridine *N*-oxide) and fluoroarenes with enantioenriched chiral secondary *Z*-allylic phosphates occurred in the presence of a stoichiometric amount of LiO*t*Bu as a base with excellent S_N2'-type regioselectivity and 1,3-*anti* stereospecificity. The reaction afforded chiral secondary alkylated (hetero)arenes.[9] Herein we report copper-catalyzed enantioselective allylic alkylation of azoles, which are electron-deficient heteroarenes, with γ,γ-disubstituted primary allylic phosphates to form a controlled all-carbon quaternary stereogenic center at the position α to the heteroaromatic ring.[10,11] The reaction was enabled by employing a stoichiometric amount of LiO*t*Bu as a base and a catalytic amount of a copper(I) complex with a new chiral N-heterocyclic carbene (NHC) ligand bearing a naphthol group.

In our previous investigation of copper-catalyzed enantioselective allylic alkylation of terminal alkyne pronucleophiles, we found that chiral NHCs bearing a phenolic hydroxy group at the *ortho* position of one of the two N-aryl groups were effective ligands.[12] Based on this, the NHC ligand **L1**, which exhibited high performance in the our previous study of copper catalysis, was initially used in the reaction between benzothiazole (**1a**; 1.5 equiv) and the *E*-allylic phosphate (*E*)-**2a** in the presence of CuCl (10 mol%) and LiO*t*Bu (2.2 equiv) in 1,4-dioxane at 25 °C (Table 1, entry 1). The copper/**L1** complex, prepared in situ from **L1**·HBF_4, CuCl, and LiO*t*Bu, induced excellent branch selectivity (b/l > 99:1), but unfortunately, catalytic activity and enantioselectivity were low (24 h, 35% yield, 15% *ee*).[13] To our delight, however, changing the phenol group of **L1** to a naphthol group, to give the new ligand **L2**, caused marked increases in product yield (77%) and enantioselectivity (68%), with the exclusive regioselectivity unchanged (entry 2). Next, we prepared a series of phenol- or naphthol-based chiral NHC ligands and screened them for suitability in this enantioselective copper catalysis. The chiral NHC ligand **L3**, bearing a *N*-2,4-dicyclohexyl-6-methylphenyl group instead of the N-mesityl group in **L2**, gave even better enantioselectivity (81% *ee*), at the cost of a slight reduction in product yield (entry 3). Changing the hydroxy group of **L3** to a methoxy group was unfavorable for both product yield and branch regioselectivity, although the reduction in enantioselectivity was not significant (entry 5). In contrast to the results obtained using oxygen-functionalized NHC ligands, no reaction occurred with either NHC ligands lacking an oxygen functional group, such as **L5**, IMes, and SIMes, or without exogenous ligand (entries 6–9). Thus, functional roles were suggested for the OH and OMe groups in **L3** and **L4**, respectively, as in the case of copper-catalyzed enantioselective allylic alkylation of terminal alkynes.[12]

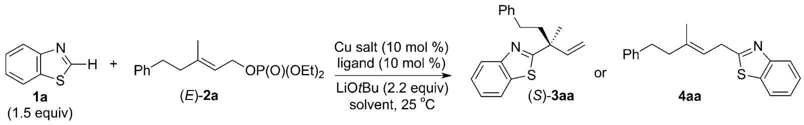
Using **L3** as an optimal chiral ligand, the effects of solvents were examined (Table 1, entries 10–13). The use of THF as a solvent instead of 1,4-dioxane resulted in higher product yield and enantioselectivity (66% and 83% *ee*) (entry 10). The use of CH_3CN as a solvent increased the enantioselectivity (88% *ee*) of the reaction, but with a reduction in the yield (50%; entry 11). The reaction proceeded more efficiently in a mixed solvent system of THF/CH_3CN (3:1), with the enantioselectivity unchanged (entry 12). Even

---

[*] Prof. Dr. H. Ohmiya, H. Zhang, S. Shibata, A. Harada,
Prof. Dr. M. Sawamura
Department of Chemistry, Faculty of Science
Hokkaido University, Sapporo 060–0810 (Japan)
E-mail: ohmiya@sci.hokudai.ac.jp
sawamura@sci.hokudai.ac.jp
Homepage: http://wwwchem.sci.hokudai.ac.jp/~orgmet/index.php

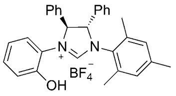
Supporting information for this article can be found under:
http://dx.doi.org/10.1002/anie.201600619.

Table 1: Copper-catalyzed enantioselective allylic alkylation of benzothiazole (**1a**) with (*E*)-allylic phosphate **2a**.[a]

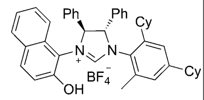


Entry	Cu salt	Ligand	Solvent	Yield [%][b]	b/l (**3aa**/**4aa**)[c]	(*S*)-**3aa** *ee* [%][d]
1	CuCl	**L1**	1,4-dioxane	35	> 99:1	15
2	CuCl	**L2**	1,4-dioxane	77	> 99:1	68
3	CuCl	**L3**	1,4-dioxane	57	> 99:1	81
4[e,h]	CuCl	**L3**	1,4-dioxane	60	> 99:1	88
5	CuCl	**L4**	1,4-dioxane	29	94:6	76
6	CuCl	**L5**	1,4-dioxane	0	–	–
7	CuCl	IMes[f]	1,4-dioxane	0	–	–
8	CuCl	SIMes[g]	1,4-dioxane	0	–	–
9	CuCl	none	1,4-dioxane	0	–	–
10	CuCl	**L3**	THF	66	> 99:1	83
11	CuCl	**L3**	MeCN	50	> 99:1	88
12	CuCl	**L3**	THF/MeCN	54	> 99:1	88
13	$[Cu(CH_3CN)_4]PF_6$	**L3**	THF/MeCN	46	> 99:1	91
14[e,i]	$[Cu(CH_3CN)_4]PF_6$	**L3**	THF/MeCN	38	> 99:1	93

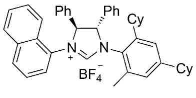
[a] Reactions were carried out with **1a** (0.225 mmol), **2a** (0.15 mmol), a Cu salt (10 mol%), the appropriate ligand (10 mol%), and Li*Ot*Bu (0.33 mmol) in the appropriate solvent (0.4 mL) at 25 °C for 24 h unless otherwise noted. [b] Yield of isolated product. [c] The ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The enantiomeric excess was determined by HPLC analysis. [e] **2a** was added in portions (4 times) to the mixture of **1a**, the Cu salt, **L3**, Li*Ot*Bu and solvent at intervals of 4 h and the resulting mixture was stirred for 36 h. [f] IMes·HCl [1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride] was used. [g] SIMes·HCl [1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride] was used. [h] Conditions A. [i] Conditions B.



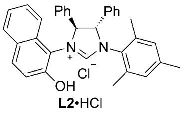
L1•HBF4



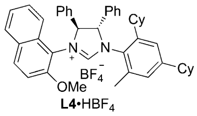
L3•HBF4



L5•HBF4



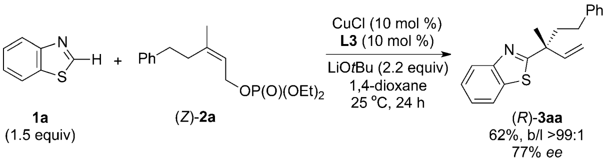
L2•HCl



L4•HBF4

higher enantioselectivity (91%) was obtained when $[Cu(CH_3CN)_4]PF_6$ was used as a metal source (entry 13). Further improvements in enantioselectivity were achieved by the addition of (*E*)-**2a** portionwise. The reactions of the CuCl/**L3**/Li*Ot*Bu/1,4-dioxane (Table 1, entry 4, conditions A) and $[Cu(CH_3CN)_4]PF_6$/**L3**/Li*Ot*Bu/THF/MeCN (entry 14, conditions B) systems gave *ee* values of 88 and 93%, respectively.

The reaction of (*Z*)-**2a** under the reaction conditions shown in Table 1, entry 3, provided (*R*)-**3aa**, the antipode of the product derived from (*E*)-**2a**, with 77% *ee* in 62% yield and with excellent branch selectivity (> 99:1) [Eq. (1)]. This



(1)

result suggests that *E* alkenes are more favorable substrates than *Z* alkenes and that the substitution pattern at the β-carbon atom is more important than that at the γ-carbon atom for enantiodiscrimination by the catalyst.

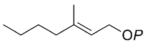
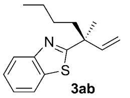
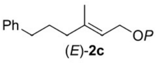
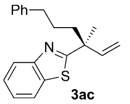
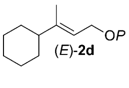
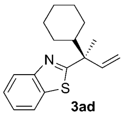
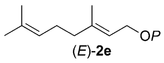
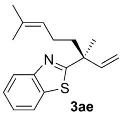
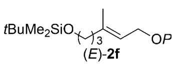
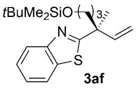
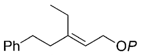
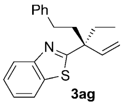
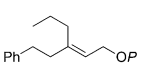
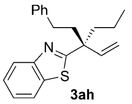
The copper-catalyzed allylic alkylation reaction afforded various azole products containing α-quaternary carbon stereogenic centers.[14–17] All of the reactions listed in Tables 2 and 3 were conducted under both sets of reaction conditions (A and B). Product yields were generally higher under the reaction conditions A, while enantioselectivity was better under the reaction conditions B in most cases (Table 2, entries 1, 2 , and 4–6, and Table 3, entries 1, 2, 4, 5, and 6).

Table 2 summarizes the results of the reactions of **1a** with various (*E*)-γ,γ-disubstituted allylic phosphates [(*E*)-**2b**–**h**]. Replacement of the phenylethyl γ-substituent of (*E*)-**2a** with butyl [(*E*)-**2b**] or phenylpropyl [(*E*)-**2c**] groups did not affect the reactivity and enantioselectivity significantly (entries 1 and 2). Remarkably, the allylic phosphate [(*E*)-**2d**], with a more sterically demanding cyclohexyl group at the γ-position, also participated in the reaction, thus giving the 2-alkylbenzothiazole **3ad**, which has a quaternary stereogenic center, with considerable steric congestion (entry 3). Alkene [(*E*)-**2e**] or silyl ether [(*E*)-**2f**] moieties in the aliphatic γ-substituent were compatible with the reaction (entries 4 and 5). This protocol is useful for the construction of quaternary stereogenic centers substituted with different alkyl groups of nearly equal steric demand, as indicated by the results using ethyl- [(*E*)-**2g**] or propyl-substituted [(*E*)-**2h**] allylic phosphates (entries 6 and 7).

Other azole-type heteroarenes also participated in the enantioselective allylic alkylation reaction (Table 3). The presence of MeO (**1b**) or Me (**1c**) groups at the 6-position of the benzene ring of benzothiazole did not affect the reaction, as demonstrated in the reactions using (*E*)-**2a** (entries 1 and 2). Benzoxazole (**1d**) and 5-chlorobenzoxazole (**1e**) reacted with reasonably high enantioselectivity (entries 3 and 4). The reactions of 4-phenyloxazole (**1f**) occurred with a useful level of enantioselectivity, albeit with decreased branch regioselectivity (entries 5 and 6, footnotes e–h). A reason for the lower regioselectivities of the reactions with this specific substrate (**1f**) is not clear at present.

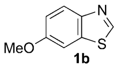
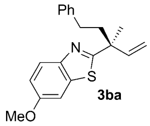
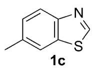
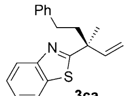
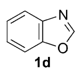
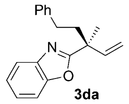
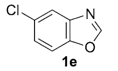
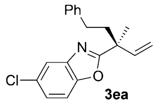
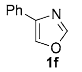
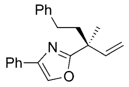
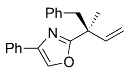
The absolute configuration of (−)-**3fi** (Table 3, entry 6) was determined to be *S* by conducting an alternative synthesis of this compound from a known compound having a quaternary stereogenic center [(*S*)-**5**], which was prepared through

Table 2: Copper-catalyzed enantioselective allylic alkylation with various allylic phosphates.[a]

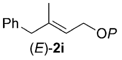
Entry	Phosphate $OP = OP(O)(OEt)_2$	Product	Cond. A		Cond. B	
			Yield [%][b,c]	*ee* [%][d]	Yield [%][b,c]	*ee* [%][d]
1	 (*E*)-**2b**	 **3ab**	51	83	25	91
2	 (*E*)-**2c**	 **3ac**	69	82	43	91
3	 (*E*)-**2d**	 **3ad**	47[e]	90	36	86
4	 (*E*)-**2e**	 **3ae**	70	83	51	89
5	 (*E*)-**2f**	 **3af**	48	78	23	87
6	 (*E*)-**2g**	 **3ag**	46	85	23	84
7	 (*E*)-**2h**	 **3ah**	39	81	24	79

[a] Conditions A: the reaction was carried out with **1a** (0.225 mmol), **2** (0.15 mmol), CuCl (10 mol%), **L3** (10 mol%), and LiO*t*Bu (0.33 mmol) in 1,4-dioxane (0.4 mL) at 25 °C. Conditions B: the reaction was carried out with **1a** (0.225 mmol), **2** (0.15 mmol), $[Cu(CH_3CN)_4]PF_6$ (10 mol%), **L3** (10 mol%), and LiO*t*Bu (0.33 mmol) in THF/MeCN (3:1, 0.4 mL) at 25 °C. **2** was added in portions (4 times) to the mixture of **1a**, the Cu salt, **L3**, LiO*t*Bu and solvent at intervals of 4 h, and the resulting mixture was stirred for 36 h. [b] Yield of isolated product. [c] Constitutional isomer ratio b/l > 99:1 (determined by ^1H NMR analysis of the crude reaction mixture). [d] The enantiomeric excess was determined by HPLC analysis. [e] b/l 96:4.

Table 3: Copper-catalyzed enantioselective allylic alkylation with various azoles.[a]

Entry	Azole	Phos-phate	Product	Cond. A		Cond. B	
				Yield [%][b,c]	*ee* [%][d]	Yield [%][b,c]	*ee* [%][d]
1	 **1b**	(*E*)-**2a**	 **3ba**	69	86	40	92
2	 **1c**	(*E*)-**2a**	 **3ca**	60	90	39	93
3	 **1d**	(*E*)-**2a**	 **3da**	48	83	24	81
4	 **1e**	(*E*)-**2a**	 **3ea**	17	74	6	82
5	 **1f**	(*E*)-**2a**	 **3fa**	86[e]	77	87[f]	66
6	**1f**	(*E*)-**2i**[i]	 **3fi**	46[g]	69	16[h]	78

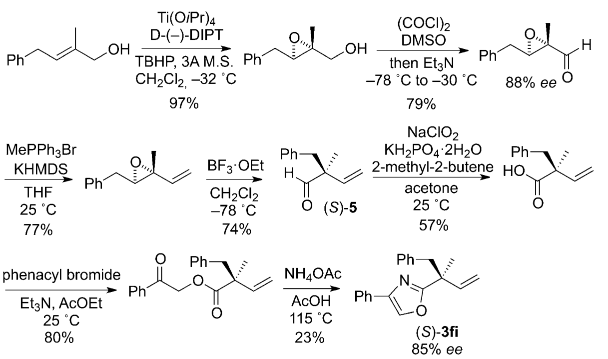
[a] Conditions A: the reaction was carried out with **1** (0.225 mmol), **2** (0.15 mmol), CuCl (10 mol%), **L3** (10 mol%), and LiO^{t}Bu (0.33 mmol) in 1,4-dioxane (0.4 mL) at 25 °C. Conditions B: the reaction was carried out with **1** (0.225 mmol), **2** (0.15 mmol), $[Cu(CH_3CN)_4]PF_6$ (10 mol%), **L3** (10 mol%), and LiO*t*Bu (0.33 mmol) in THF/MeCN (3:1, 0.4 mL) at 25 °C. **2** was added in portions (4 times) to the mixture of **1**, the Cu salt, **L3**, LiO*t*Bu and solvent at intervals of 4 h, and the resulting mixture was stirred for 36 h. [b] Yield of isolated product. [c] Constitutional isomer ratio b/l > 99:1 (determined by ^1H NMR analysis of the crude reaction mixture). [d] The enantiomeric excess was determined by HPLC analysis. [e] b/l 90:10. [f] b/l 54:46. [g] b/l 96:4. [h] b/l 67:33. [i]


(*E*)-**2i**

$OP = OP(O)(OEt)_2$

Sharpless asymmetric epoxidation and subsequent Lewis-acid-mediated epoxide-to-aldehyde rearrangement (Scheme 1).[17] Absolute configurations of the other allylic alkylation products (**3**), which are not accessible with the same method except for (*S*)-**3fa** (Table 3, entry 5), were assigned by consideration of the stereochemical pathway. The lengthy synthesis of (*S*)-**5** through a conventional route (Scheme 1) demonstrates the difficulty of the synthesis of tertiary alkylated heteroarenes and highlights efficacy of the present convergent method enabled by the enantioselective copper catalysis.

In summary, we developed a copper-catalyzed branch and enantioselective allylic alkylation reaction of azoles with γ,γ-disubstituted primary allylic phosphates to form a controlled all-carbon quaternary stereogenic center at the position α to the heteroaromatic ring, by introducing a new chiral N-heterocyclic carbene ligand bearing a naphtholic hydroxy group. Thus, enantiocontrolled introduction of tertiary alkyl groups to heteroarenes through $C(sp^2)$–H functionalization



Scheme 1. Synthesis of (*S*)-**3fi** through Sharpless asymmetric epoxidation, epoxide-to-aldehyde rearrangement, and oxazole formation (determination of the absolute configuration). DMSO = dimethylsulfoxide, KHMDS = potassium hexamethyldisilazide, DIPT = diisopropyl tartrate, TBHP = *tert*-butylhydroperoxide, THF = tetrahydrofuran.

was achieved. Mechanistic studies of this enantioselective copper catalysis and its comparison with the corresponding reaction using terminal alkynes as pronucleophiles are in progress.[12]

Acknowledgments

This work was supported by Grants-in-Aid for Scientific Research (B) (No. 15H03803), JSPS, to H.O. and by CREST and ACT-C, JST, to M.S.

Keywords: allylic compounds · asymmetric catalysis · carbenes · copper · heterocycles

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 4777–4780
Angew. Chem. **2016**, *128*, 4855–4858

---

[1] For reviews, see: a) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593; b) I. Marek, Y. Minko, M. Pasco, T. Mejuch, N. Gilboa, H. Chechik, J. P. Das, *J. Am. Chem. Soc.* **2014**, *136*, 2682; c) K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181.

[2] a) H. Qiu, M. Li, L.-Q. Jiang, F.-P. Lv, L. Zan, C.-W. Zhai, M. P. Doyle, W.-H. Hu, *Nat. Chem.* **2012**, *4*, 733; b) D. Zhang, H. Qiu, L. Jiang, F. Lv, C. Ma, W.-H. Hu, *Angew. Chem. Int. Ed.* **2013**, *52*, 13356; *Angew. Chem.* **2013**, *125*, 13598.

[3] For Friedel–Crafts-type reactions, see: a) D. Łyżwa, K. Dudziński, P. Kwiatkowski, *Org. Lett.* **2012**, *14*, 1540; b) K. Mori, M. Wakazawa, T. Akiyama, *Chem. Sci.* **2014**, *5*, 1799; c) W. Zhao, Z. Wang, B. Chu, J. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 1910; *Angew. Chem.* **2015**, *127*, 1930; d) Z. Wang, F. Ai, Z. Wang, W. Zhao, G. Zhu, Z. Lin, J. Su, *J. Am. Chem. Soc.* **2015**, *137*, 383; e) J.-R. Gao, H. Wu, B. Xiang, W.-B. Yu, L. Han, Y.-X. Jia, *J. Am. Chem. Soc.* **2013**, *135*, 2983; f) M. Bandini, A. Melloni, F. Piccinelli, R. Sinisi, S. Tommasi, A. Umani-Ronchi, *J. Am. Chem. Soc.* **2006**, *128*, 1424.

[4] Oestreich and co-workers achieved moderate enantioselectivity in the construction of all-carbon quaternary stereogenic centers through palladium-catalyzed enantioselective intramolecular Fujiwara–Moritani reactions of indoles or pyrroles. See: a) J. A. Schiffner, A. B. Machotta, M. Oestreich, *Synlett* **2008**, 2271; b) J. A. Schiffner, T. H. Wöste, M. Oestreich, *Eur. J. Org. Chem.* **2010**, 174.

[5] C. Zhang, C. B. Santiago, J. M. Crawford, M. S. Sigman, *J. Am. Chem. Soc.* **2015**, *137*, 15668.

[6] For reviews of enantioselective C–H functionalization, see: a) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242; b) J. Wencel-Delord, F. Colobert, *Chem. Eur. J.* **2013**, *19*, 14010; c) C. Zheng, S.-L. You, *RSC Adv.* **2014**, *4*, 6173; d) B. Ye, N. Cramer, *Acc. Chem. Res.* **2015**, *48*, 1308.

[7] For selected papers on the construction of tertiary carbon stereogenic centers through enantioselective C–H functionalization of heteroarenes, see: a) S. Pan, N. Ryu, T. Shibata, *J. Am. Chem. Soc.* **2012**, *134*, 17474; b) C. S. Sevov, J. F. Hartwig, *J. Am. Chem. Soc.* **2013**, *135*, 2116; c) G. Song, W. W. N. O, Z. Hou, *J. Am. Chem. Soc.* **2014**, *136*, 12209; d) P.-S. Lee, N. Yoshikai, *Org. Lett.* **2015**, *17*, 22.

[8] For enantioselective construction of all-carbon quaternary stereogenic centers through metal-catalyzed intramolecular C–H functionalization of arenes, see: B. Ye, P. A. Donets, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 507; *Angew. Chem.* **2014**, *126*, 517. The work by Hu and co-workers (Ref. [2a]) also involved construction of all-carbon quaternary stereogenic centers through intramolecular C(sp^2)–H alkylation of diazo-functionalized anilide derivatives.

[9] Y. Makida, H. Ohmiya, M. Sawamura, *Angew. Chem. Int. Ed.* **2012**, *51*, 4122; *Angew. Chem.* **2012**, *124*, 4198.

[10] For reviews on copper-catalyzed enantioselective allylic substitutions, see: a) C. A. Falciola, A. Alexakis, *Eur. J. Org. Chem.* **2008**, 3765; b) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796; c) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824.

[11] For enantioselective constructions of all-carbon quaternary stereogenic centers through copper-catalyzed allylic substitutions using organometallic reagents and oxygen-functionalized NHC chiral ligands, see: a) F. Gao, K. P. McGrath, Y. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 14315; b) F. Gao, Y. Lee, K. Mandai, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2010**, *49*, 8370; *Angew. Chem.* **2010**, *122*, 8548; c) R. Shintani, K. Takatsu, M. Takeda, T. Hayashi, *Angew. Chem. Int. Ed.* **2011**, *50*, 8656; *Angew. Chem.* **2011**, *123*, 8815; d) B. Jung, A. H. Hoveyda, *J. Am. Chem. Soc.* **2012**, *134*, 1490; e) F. Gao, J. L. Carr, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2012**, *51*, 6613; *Angew. Chem.* **2012**, *124*, 6717; f) Y. Shi, B. Jung, S. Torker, A. H. Hoveyda, *J. Am. Chem. Soc.* **2015**, *137*, 8948.

[12] a) A. Harada, Y. Makida, T. Sato, H. Ohmiya, M. Sawamura, *J. Am. Chem. Soc.* **2014**, *136*, 13932. See also: b) Y. Makida, Y. Takayama, H. Ohmiya, M. Sawamura, *Angew. Chem. Int. Ed.* **2013**, *52*, 5350; *Angew. Chem.* **2013**, *125*, 5458.

[13] No reaction occurred with either 1,10-phenanthroline, PPh_3, or DPPE.

[14] The reaction of γ-monosubstituted allylic phosphates did not give the corresponding alkylated azole products, but gave trisubstituted alkenes which were isomerized from the products and conjugate dienes which stemmed from the allylic phosphates.

[15] For Tables 1–3 and Equation (1), the crude materials after removal of the catalyst consisted of the alkylated azole product **3**, unreacted azole **1**, and conjugated dienes. The dienes could easily be separated from **3** by silica-gel chromatography.

[16] The enantiomeric purities of solid products (**3aa**, **3ba**, **3fa**, **3fi**) did not increase upon recrystallization.

[17] M. E. Jung, D. C. D'Amico, *J. Am. Chem. Soc.* **1995**, *117*, 7379.

Received: January 20, 2016