Allylic Alkylation

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Regio- and Stereocontrolled Introduction of Secondary Alkyl Groups to Electron-Deficient Arenes through Copper-Catalyzed Allylic Alkylation**

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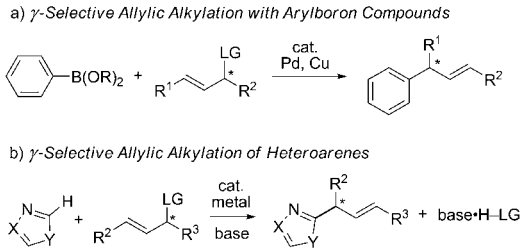
Heteroarenes are important structural motifs found in many pharmaceuticals, agrochemicals and natural products.[1] Accordingly, the development of efficient methods for heteroarene functionalization is important. Although there are various methods for accessing functionalized heteroarenes, the C-alkylation of these species is still severely limited in scope. Indeed, conventional methods involving stoichiometric metalation of electron-deficient heteroarenes followed by trapping with alkyl halides or pseudo halides are generally difficult because heteroarylmetal species are unstable compared with arylmetals.[2] Friedel–Crafts-type reactions also allow for alkylation, but these methods are only applicable to electron-rich heteroarenes.[3] Recently, transition-metal-catalyzed C_{sp^2}–H functionalizations of (hetero)arenes, such as alkene hydro(hetero)arylations[4,5] or couplings with alkyl halides,[6,7] have been introduced as new approaches for heteroarene C-alkylation. However, even with these methods the introduction of secondary alkyl groups is quite difficult.[5,8] In particular, the stereocontrolled introduction of a secondary alkyl group remains underdeveloped, although it was achieved in the intramolecular alkene hydroarylations of Ellman, Bergman and co-workers.[9]

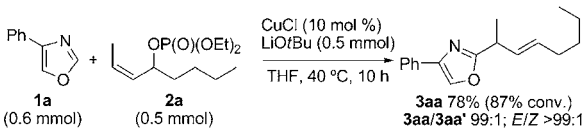
Earlier, we reported organoboron-based Pd^{II}- or Cu^{I}-catalyzed approaches for the allylic alkylation of arenes (Scheme 1a).[10] High γ-regioselectivity, 1,3-*anti* or *syn* stereoselectivities, and broad functional group compatibilities are all attractive features of these approaches. Therefore, the extension of these organoboron-based approaches to the alkylation of heteroarenes might be expected. We did not take this approach, however, because we knew that α-borylheteroarenes are generally unstable and difficult to prepare. Instead, we envisioned that the base-assisted direct cupration of heteroarenes under the conditions of Daugulis might be effective and more straightforward for the catalytic generation of heteroarylcopper(I) species that are reactive in the γ-selective allyl–aryl coupling (Scheme 1b).[11]



Scheme 1. γ-Selective allyl–aryl or allyl–heteroaryl couplings. LG = leaving group.

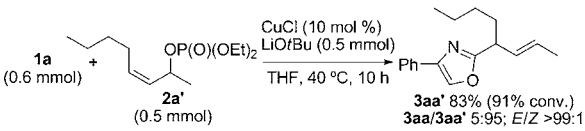
Herein we report a Cu-catalyzed allylic alkylation of electron-deficient heteroarenes with internal secondary allylic phosphates, which proceeded with excellent γ-regioselectivity and *E*-stereoselectivity.[12–15] This copper catalyst system was similarly applicable to fluoroarenes. Furthermore, the reaction of enantioenriched secondary allylic phosphates proceeded with 1,3-*anti* stereoselectivity to afford the corresponding alkylated (hetero)arenes with a controlled secondary stereogenic center. Thus, this Cu-catalyzed alkylation is a straightforward method for the stereocontrolled introduction of secondary alkyl groups to electron-deficient (hetero)arenes.

Specifically, the γ-substitution reaction of 4-phenyloxazole (**1a**; 0.6 mmol) with *Z* allylic phosphate **2a** (0.5 mmol) in the presence of CuCl (10 mol%) and LiO*t*Bu (0.5 mmol) in THF (1 mL) at 40 °C for 10 h afforded alkylated arene product **3aa** in 78% yield (87% conversion) with excellent regio- (**3aa**/**3aa′** 99:1) and stereoselectivities (*E*/*Z* > 99:1) [Eq. (1)].[16,17] On the other hand, the reaction of the isomeric



(1)

substrate **2a′** proceeded with slightly decreased γ-selectivity to afford **3aa** and **3aa′** in a 5:95 ratio [Eq. (2)]. The slight



(2)

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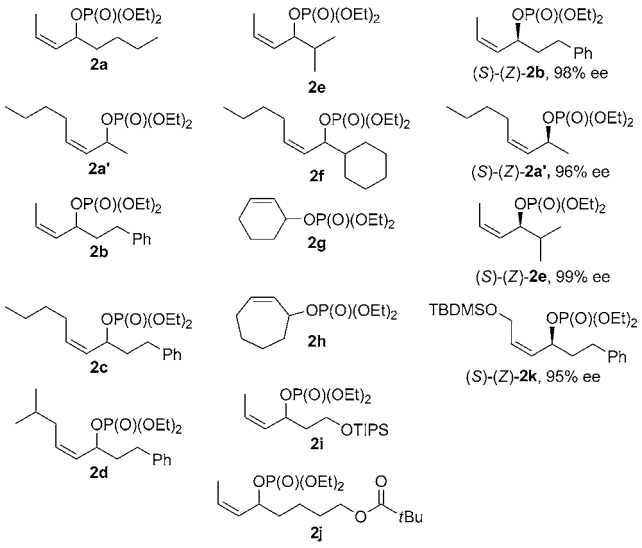
difference in the regioselectivities of the isomeric substrates indicates that the relative steric demands of the α- and γ-substituents perturb the regioselectivity to some extent. However, these results indicate that a useful level of γ-selectivity is obtainable, even when unfavorable steric effects are present.

Several observations concerning the optimum reaction conditions for the reaction between **1a** and **2a′**, [Eq. (2)] are to be noted: No reaction occurred when KO*t*Bu was used as a base or in the absence of CuCl. The use of CuOAc, CuOTf, or CuI instead of CuCl resulted in decreased yields and regioselectivities (70%, 12:88; 73%, 13:87; 71%, 23:77, respectively). Also, allylic substrates with carbonate or acetate leaving groups were not reactive at all.

The steric effects of the α- and γ-substituents of allylic phosphates **2** (Scheme 2) on the reactivity and regioselectivity



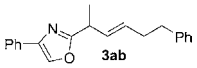
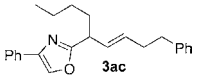
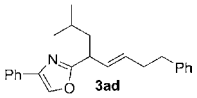
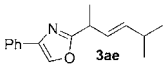
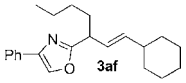
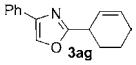
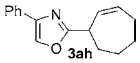
Scheme 2. Allylic phosphates used. TIPS = triisopropylsilyl, TBDMS = *tert*-butyldimethylsilyl.

were further evaluated and the results are shown in Table 1, entries 1–5.[18] As the γ-substituent became bulkier (Me < Bu < *i*Bu), the regioselectivity gradually decreased (99 > 96 > 92%) with decreasing product yields (81 > 73 > 63%; entries 1–3). On the other hand, allylic phosphates **2e** and **2f**, bearing sterically more demanding groups (*i*Pr or cyclohexyl) in place of the α-$PhCH_2CH_2$ substituent of **2b**, underwent the reaction with excellent γ-selectivity (> 99:1; entries 4 and 5).

Cyclic allylic phosphates also served as substrates (Table 1, entries 6 and 7). Oxazole **1a** reacted with 2-cyclohexenyl phosphate (**2g**) to provide the product in a decent yield (53%; entry 6). The reaction of **1a** with seven-membered cyclic phosphate **2h** was more effective, providing the product in 92% yield (entry 7).

The Cu-catalyzed allylation was applicable to a range of heteroarenes (**1**) and allylic phosphates (**2**) as shown in Table 2. Functional groups on **1** or **2**, such as silyl ethers,

Table 1: Cu-catalyzed allylic alkylation with **1a**.[a]

Entry	Arene	Phosphate	Product[b]	Yield [%][c]	γ/α[d]
1	**1a**	**2b**	 **3ab**	81	> 99:1
2	**1a**	**2c**	 **3ac**	73	96:4
3	**1a**	**2d**	 **3ad**	63	92:8
4[e]	**1a**	**2e**	 **3ae**	45	> 99:1
5[f]	**1a**	**2f**	 **3af**	61	> 99:1
6	**1a**	**2g**	 **3ag**	53	–
7	**1a**	**2h**	 **3ah**	92	–

[a] Reaction conditions: **1a** (0.24 mmol), **2** (0.2 mmol), CuCl (10 mol%), Li*O*t*Bu (0.2 mmol) in THF (0.4 mL) at 40°C for 10 h. [b] Isomeric ratio (*E*/*Z*) > 99:1. [c] Yield of isolated product. [d] Determined by ^{1}H NMR or GC analysis of the crude product. [e] The reaction was carried out at 60°C. [f] The reaction was carried out on a 1.0 mmol scale at 60°C.

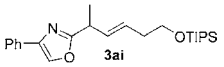
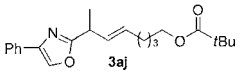
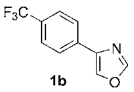
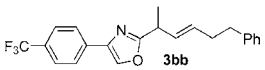
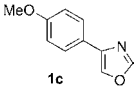
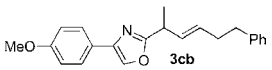
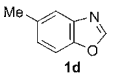
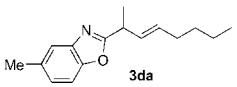
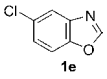
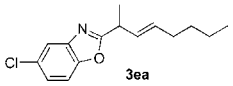
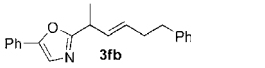
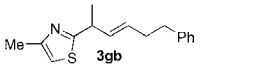
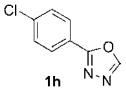
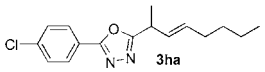
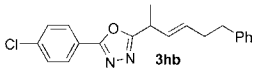
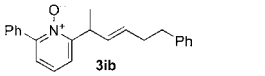
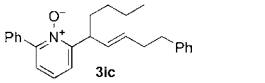
esters, CF_3, MeO, and Cl, were also compatible (Table 2, entries 1–4, 6, and 9–11).

Various azole derivatives were used (Table 2).[19] The reaction of 4-phenyloxazole derivative **1b** with a CF_3 substituent at the *para* position of the phenyl group occurred with a high γ-selectivity (97:3; entry 3). Substitution with a MeO group (**1c**), however, decreased the γ-selectivity to 88% (entry 4). Benzoxazole derivatives **1d** and **1e** were effective in the reaction with **2a** and afforded **3da** and **3ea**, respectively, with 96% γ-selectivity (entries 5 and 6). Ring substitution with a Ph group was also tolerated at the 5-position of the oxazole, as shown in the reaction of **1f** (entry 7). A sulfur-containing heterocycle, 4-methylthiazole (**1g**), reacted in moderate yield (60%) with excellent γ-regioselectivity (> 99:1; entry 8). The reaction between 2-(4-chlorophenyl)-1,3,4-oxadiazole (**1h**) and **2a** afforded **3ha** in 83% yield with 95% γ-regioselectivity (entry 9). The oxadiazole **1h** reacted with **2b** in 96% γ-selectivity (entry 10).

The method was also applicable to a pyridine *N*-oxide derivative (entries 11 and 12). The reaction of 2-phenylpyridine *N*-oxide (**1i**) with **2b** occurred at the 6-position of the pyridine to afford the corresponding product **3ib** in high yield (92%) with excellent γ-selectivity (> 99:1; entry 11). Replacing the γ-Me substituent of **2b** with a sterically more demanding butyl group (**2c**) did not affect the excellent γ-selectivity (> 99:1; entry 12).

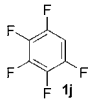
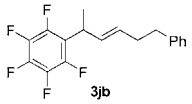
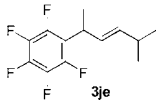
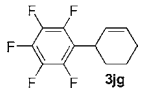
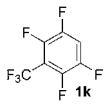
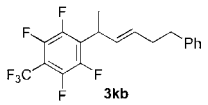
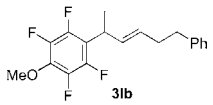
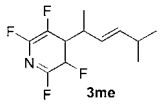
The copper-catalyzed method has also been extended to the reaction of fluoroarenes (Table 3). Pentafluorobenzene (**1j**) reacted efficiently with **2b** to afford **3jb** in 93% yield with 90% γ-selectivity (entry 1). The reaction of **1j** with the α-isopropyl allylic phosphate **2e** showed excellent regioselectivity (87% yield, γ/α > 99:1; entry 2). The cyclic allylic

Table 2: Cu-catalyzed allylic alkylation with various heteroarenes.[a]

Entry	Arene	Phosphate	Product[b]	Yield [%][c]	γ/α[d]
1	**1a**	**2i**	 **3ai**	61	>99:1
2	**1a**	**2j**	 **3aj**	80	>99:1
3	 **1b**	**2b**	 **3bb**	82	97:3
4	 **1c**	**2b**	 **3cb**	55	88:12
5	 **1d**	**2a**	 **3da**	77	96:4
6	 **1e**	**2a**	 **3ea**	50	96:4
7	 **1f**	**2b**	 **3fb**	52[f]	>99:1
8[e]	 **1g**	**2b**	 **3gb**	60	>99:1
9	 **1h**	**2a**	 **3ha**	83	95:5
10	**1h**	**2b**	 **3hb**	86	96:4
11	 **1i**	**2b**	 **3ib**	92	>99:1
12	**1i**	**2c**	 **3ic**	60	>99:1

[a] Reaction conditions: **1** (0.24 mmol), **2** (0.2 mmol), CuCl (10 mol%), LiO*t*Bu (0.2 mmol) in THF (0.4 mL) at 40°C for 10 h. [b] Isomeric ratio (*E*/*Z*) >99:1. [c] Yield of isolated product. [d] Determined by ^{1}H NMR or GC analysis of the crude product. [e] The reaction was carried out at 60°C. [f] Yield determined by NMR analysis. Significant amounts of unidentified compounds were also detected.

Table 3: Cu-catalyzed allylic alkylation with various fluoroarenes.[a]

Entry	Arene	Phosphate	Product[b]	Yield [%][c]	γ/α[d]
1	 **1j**	**2b**	 **3jb**	93	90:10
2	**1j**	**2e**	 **3je**	87	>99:1
3	**1j**	**2g**	 **3jg**	78	–
4	 **1k**	**2b**	 **3kb**	88	94:6
5	 **1l**	**2b**	 **3lb**	67	92:8
6[e]	 **1m**	**2e**	 **3me**	73	>99:1

[a] Reaction conditions: **1** (0.24 mmol), **2** (0.2 mmol), CuCl (10 mol%), LiO*t*Bu (0.2 mmol) in THF (0.4 mL) at 40°C for 10 h. [b] Isomeric ratio (*E*/*Z*) >99:1. [c] Yield of isolated product. [d] Determined by ^{1}H NMR or GC analysis of the crude product. [e] The reaction was carried out in toluene.

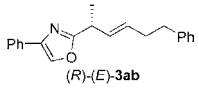
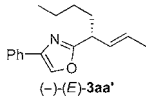
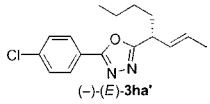
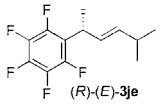
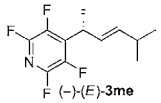
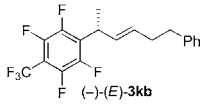
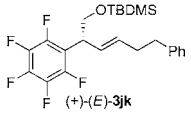
phosphate **2g** coupled with **1j** to give the product in good yield (entry 3). The tetrafluoroarenes **1k** and **1l**, bearing CF_3 and MeO groups, respectively, and 2,3,5,6-tetrafluoropyridine (**1m**) also served as suitable fluoroarene substrates (entries 4–6).

The alkylation of azole derivatives with enantioenriched allylic phosphates proceeded with 1,3-*anti* stereochemistry, allowing the stereocontrolled introduction of secondary alkyl groups (Table 4, entries 1–3). Specifically, the alkylation of 4-phenyloxazole (**1a**) with (*S*)-(*Z*)-**2b** (98% *ee*), which has α-$PhCH_2CH_2$ and γ-Me substituents, proceeded with 90% *anti* stereoselectivity, affording (*R*)-(*E*)-**3ab** with 79% *ee* (entry 1). More efficient chirality transfer occurred in the reaction of **1a** with (*S*)-(*Z*)-**2a′** (96% *ee*), which has α-Me and γ-Bu substituents, giving (−)-(*E*)-**3aa′** with 85% *ee* (*anti*/*syn* 94:6; entry 2).[20,21] The reaction of the oxadiazole **1h** with (*S*)-(*Z*)-**2a′** (96% *ee*) afforded (−)-(*E*)-**3ha′** with 81% *ee* (*anti*/*syn* 92:8; entry 3). These results demonstrate that, despite some erosion of enantiomeric purity, the copper-catalyzed allylic alkylation allows the construction of a stereogenic center at the position α to electron-deficient heteroaromatic rings, which is rare and difficult to obtain by other methods.[9]

As shown in Table 4, entries 4–7, the reaction of fluoroarenes with enantioenriched allylic phosphates also proceeded with 1,3-*anti* stereochemistry. Specifically, the reactions of pentafluorobenzene (**1j**) or 2,3,5,6-tetrafluoropyridine (**1m**) with enantioenriched (*S*)-(*Z*)-**2e** (99% *ee*), which has α-*i*Pr and γ-Me groups gave enantioenriched (*R*)-(*E*)-**3je** (99% *ee*) and (−)-(*E*)-**3me** (95% *ee*) with 1,3-*anti* stereochemistry (*anti*/*syn* >98:2), respectively (Table 2, entries 4 and 5).[20] The reaction of the fluoroarene **1k** with (*S*)-(*Z*)-**2b** (98% *ee*) also gave excellent chirality transfer (92% *ee*, *anti*/*syn* 97:3; entry 6). The reaction of pentafluorobenzene (**1j**) with (*S*)-(*Z*)-**2k** (95% *ee*), which has a siloxymethyl group at the γ-position, afforded (+)-(*E*)-**3jk** with 90% *ee* (*anti*/*syn* 97:3; entry 7).

The active organocopper species is likely a monoorganoheterocuprate ($[ArCuO\mathit{t}Bu]^-$) rather than a neutral organocopper(I) species (L_nCuAr), because LiO*t*Bu is not basic enough to lithiate the (hetero)arenes and LiO*t*Bu is present in an excess relative to copper during the catalytic reaction.[22] This assumption is also supported by the fact that the γ-regioselectivities were generally high, but not always perfect. This rationale comes from our previous observation that the Cu-catalyzed allyl–alkyl coupling between allylic phosphates and alkylboranes occurred with perfect γ-selec-

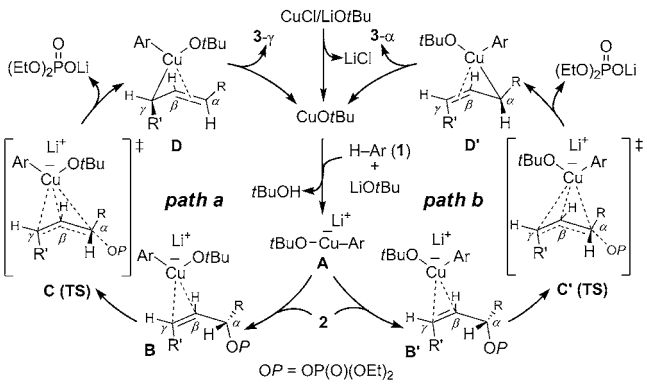
Table 4: Chirality transfer.[a]

Entry	Arene	Phosphate	Product[b]	Yield [%][c]	γ/α[d]	*ee* [%][e] (*anti*/*syn*)
1	**1a**	(*S*)-(*Z*)-**2b** 98% *ee*	 (*R*)-(*E*)-**3ab**	40	>99:1	79 (90:10)
2	**1a**	(*S*)-(*Z*)-**2a′** 96% *ee*	 (−)-(*E*)-**3aa′**	58	95:5	85 (94:6)
3	**1h**	(*S*)-(*Z*)-**2a′** 96% *ee*	 (−)-(*E*)-**3ha′**	87	88:12	81 (92:8)
4	**1j**	(*S*)-(*Z*)-**2e** 99% *ee*	 (*R*)-(*E*)-**3je**	87	>99:1	99 (>99:1)
5	**1m**	(*S*)-(*Z*)-**2e** 99% *ee*	 (−)-(*E*)-**3me**	73	>99:1	95 (98:2)
6	**1k**	(*S*)-(*Z*)-**2b** 98% *ee*	 (−)-(*E*)-**3kb**	88	94:6	92 (97:3)
7	**1j**	(*S*)-(*Z*)-**2k** 95% *ee*	 (+)-(*E*)-**3jk**	91	>99:1	90 (97:3)

[a] The reaction was carried out with **1** (0.24 mmol), **2** (0.2 mmol), CuCl (10 mol%), LiO*t*Bu (0.2 mmol) in toluene (entries 1–3 and 5; 0.4 mL) or THF (entries 4, 6, and 7; 0.4 mL) at 40°C for 10 h. [b] Isomeric ratio (*E*/*Z*) >99:1. [c] Yield of isolated product. [d] Determined by ^{1}H NMR or GC analysis of the crude product. [e] The *ee* values were determined by chiral-phase HPLC analysis.

tivity, in which neutral alkylcopper(I) species were reasonable active intermediates.[10f]

According to DFT studies by Nakamura et al. on the mechanism of the reaction between monomethylheterocuprates (Li[MeCuX]) and allyl acetate,[23] we propose the mechanism shown in Scheme 3 for the present Cu-catalyzed reaction. The catalytic cycle is initiated by a LiO*t*Bu-assisted C–H cupration of a (hetero)arene to produce a heterocuprate



Scheme 3. Possible mechanism.

([ArCuO*t*Bu]$^-$, **A**). Subsequently, **A** forms diastereomeric π-complexes **B** (path a) or **B′** (path b) with an allylic phosphate (**2**), in which the copper atom is *anti* to the leaving group (O*P*). Owing to the difference in the strength of the *trans* effect, isomer **B** is more reactive than **B′**. Thus, the oxidative addition of **B** through transition state **C(TS)** is predominant. This oxidative addition affords (σ-enyl)copper(III) species **D** (enyl[σ+π] complex), which has a C^{γ}–Cu σ bond. Finally, reductive elimination of **D** results in forming the γ-coupling product **3**-γ. The occasional incomplete γ-selectivity suggests the minor involvement of path b, in which the diastereomeric π-complex **B′** leads to enyl[σ+π] complex **D′**, which forms the α-coupling product **3**-α.

In summary, we have developed a Cu-catalyzed allylic alkylation reaction of azoles (oxazoles, an oxadiazole, and a thiazole), a pyridine *N*-oxide derivative, and fluoroarenes with internal secondary allylic phosphates that proceeds under mild reaction conditions with excellent γ and *E*-selectivities. The reaction with enantioenriched allylic phosphates proceeded with 1,3-*anti* stereoselectivity to generate an allylic stereogenic center at the position α to the aromatic ring. Accordingly, the Cu-catalyzed reaction is a straightforward and powerful method for the stereocontrolled introduction of secondary alkyl groups to electron-deficient arenes.

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[16] Allylic alcohols with a *Z* configuration are readily obtainable though *Z*-selective reductions of the corresponding propargylic alcohols.

[17] To our surprise, the *E*-isomer of **2a** showed no reactivity under the same conditions. Partial alcoholysis of **2a** to the corresponding allylic alcohol was observed.

[18] The reaction between **1a** and a *Z* allylic phosphate bearing an aryl group at the γ-position resulted in no reaction. *Z* Allylic phosphates bearing an aryl group at the α-position were too unstable to prepare.

[19] Reactions with imidazole derivatives were unsuccessful.

[20] See the Supporting Information for experiments to determine the absolute configurations of (*R*)-(*E*)-**3ab** and (*R*)-(*E*)-**3je**.

[21] Evaluation of the product enantiomeric excess values for the reactions of azole **1a** with different reaction times and conversions confirmed that no racemization of (*R*)-(*E*)-**3ab** occurred under the reaction conditions. This suggests moderate diastereotopic face selectivity in the reaction between the heteroarylcopper(I) species and the allylic phosphate. Studies

for improving the efficiency of 1,3-chirality transfer in reactions with heteroarenes are under way.

[22] Treatment of **1a** with LiO*t*Bu (1:1) in THF at 40 °C for 1 h or 10 h followed by quenching with D_2O resulted in no deuterated product. These results indicate that the heteroaryllithium does not form in a meaningful amount in the Cu-catalyzed allylic alkylation. For a discussion of the LiO*t*Bu-assisted direct cupration of electron-deficient arenes, see: Ref. [11], and references therein.

[23] a) N. Yoshikai, S.-L. Zhang, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 12862 – 12863; b) M. Yamanaka, S. Kato, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 6287 – 6293; for a review, see: c) N. Yoshikai, E. Nakamura, *Chem. Rev.* **2012**, DOI: 10.1021/cr200241f.

