C–H Functionalization

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Stereospecific Copper-Catalyzed C–H Allylation of Electron-Deficient Arenes with Allyl Phosphates**

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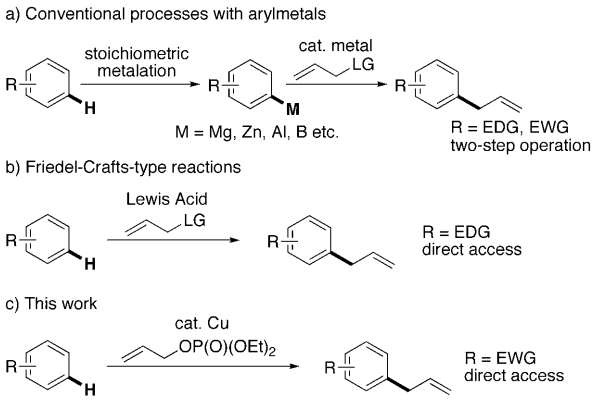
The allylation reaction is one of the most fundamental and important transformations in organic synthesis because allyl moieties are easily manipulated to access various versatile functional groups. In particular, the metal-mediated allylation of aryl metal compounds with allylic electrophiles ranks as a powerful and reliable method for the introduction of allyl units to aromatic rings. To date, various transition-metal catalysts such as copper, palladium, rhodium, and iridium have been developed to enable allyl coupling to several aryl metal compounds, including magnesium, aluminum, zinc, and boron reagents (Scheme 1 a).[1] Although valuable, the major drawback of these procedures is the inevitable preactivation step of the arenes, that is the stoichiometric metalation of the corresponding arenes or halogenated arenes. As an alternative and more straightforward approach, the Lewis acid promoted Friedel–Crafts-type reaction (Scheme 1 b) is useful because it eliminates the prior preparation of the aryl metal compounds.[2] However, this type of transformation is generally restricted in substrate scope to electron-rich arenes.[3] Thus, further developments to give more efficient and direct access to allylated electron-deficient arenes are required (Scheme 1 c).



Scheme 1. Approaches to allylarenes with allylic electrophiles. EDG = electron-donating group, EWG = electron-withdrawing group, LG = leaving group.

Recently, metal-mediated C–C bond formation by C–H functionalization has grown rapidly as a potentially more efficient and complementary process to the conventional cross-coupling methodology, and direct arylations, alkenylations, alkynylations, and alkylations have been achieved.[4] On the contrary, the corresponding allylation still remains largely elusive despite its potential.[5] Herein, we report the copper-catalyzed direct C–H allylation with allyl phosphates. The copper-based system provides a rapid and concise route to allyl arenes that contain fluorinated aromatic cores of an electron-deficient nature,[6] and are of importance in materials and life science.[7] Moreover, the unique stereospecificity of the reaction is also described.

On the basis of our recent studies on copper complexes in C–H functionalization chemistry,[8,9] we tested the copper-based systems for the direct allylation of pentafluorobenzene (**1a**; Table 1). After extensive screening of various reaction parameters, we found that the treatment of **1a** with allyl phosphate (*E*)-**2a** in the presence of a catalytic amount of [Cu(acac)$_2$]/phen and LiO*t*Bu as a base in 1,4-dioxane at room temperature afforded **3aa** in a 61 % yield with high regio- and stereoselectivity (linear/branched 98:2, *E*/*Z* 97:3; Table 1, entry 1).[10] The choice of leaving group on the allyl electrophile was crucial; the reaction of the corresponding acetate or carbonate instead of the phosphate resulted in no formation of the allylated product. Alkyl-substituted allyl phosphates bearing a silyl ether [(*E*)-**2b**] and the bulky *i*Pr group [(*E*)-**2c**] at the allylic position coupled with **1a** effectively (entries 2 and 3, respectively). Cinnamyl phosphates (*E*)-**2d–g** also underwent the reaction with regio- and stereoselectivities similar to those of the aliphatic systems (*E*)-**2a–c** (entries 4–7). Although both electron-rich and electron-deficient substituents on the benzene ring were tolerated, the methoxy-substituted reagent gave a better yield (entries 5–7). Moreover, the cyclic framework of **2h** was tolerated (entry 8).

By using the [Cu(acac)$_2$]/phen catalyst, we subsequently performed the allylation of an array of fluoroarenes (**1**; (Scheme 2). Substituted tetrafluorobenzenes with electronically diverse substituents, which included methoxy, trifluoromethyl, and cyano groups, were all compatible with the reaction conditions (**3ba**, **3bh**, **3ca**, **3ch**, and **3dh**). The coupling of the pyridine analogue also proceeded without any difficulties (**3ec** and **3eh**). In the case of 1,2,4,5-tetrafluorobenzene, the reaction occurred at both C–H bonds to provide a mixture of **3fa** and **3fa′** in a ratio of 85:15. A similar result was obtained in the reaction of 1,2,3,5-tetrafluorobenzene

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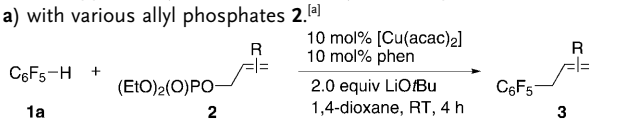
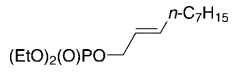
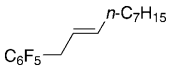
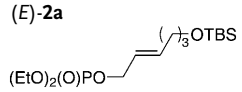
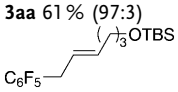
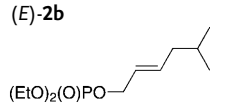
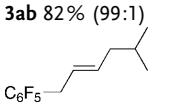
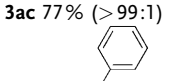
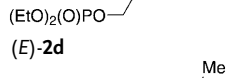
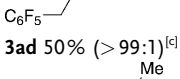
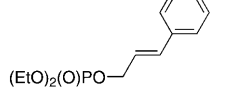
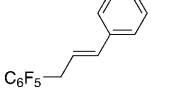
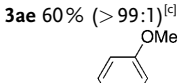
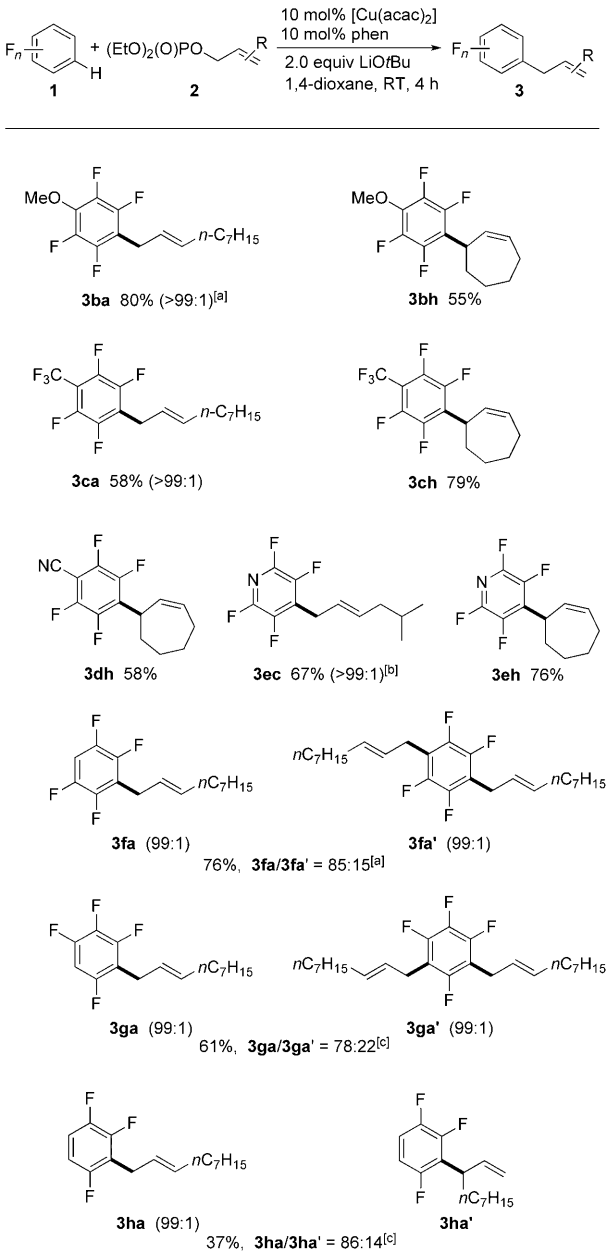
Table 1: Copper-catalyzed direct C–H allylation of pentafluorobenzene (**1a**) with various allyl phosphates **2**.[a]



Entry	**2**	**3**[b]
1	 (*E*)-**2a**	 **3aa** 61% (97:3)
2	 (*E*)-**2b**	 **3ab** 82% (99:1)
3	 (*E*)-**2c**	 **3ac** 77% (>99:1)
4	 (*E*)-**2d**	 **3ad** 50% (>99:1)[c]
5	 (*E*)-**2e**	 **3ae** 60% (>99:1)[c]
6	 (*E*)-**2f**	 **3af** 76% (>99:1)
7	 (*E*)-**2g**	 **3ag** 57% (>99:1)[c]
8	(*E*)-**2h**	**3ah** 78% (>99:1)

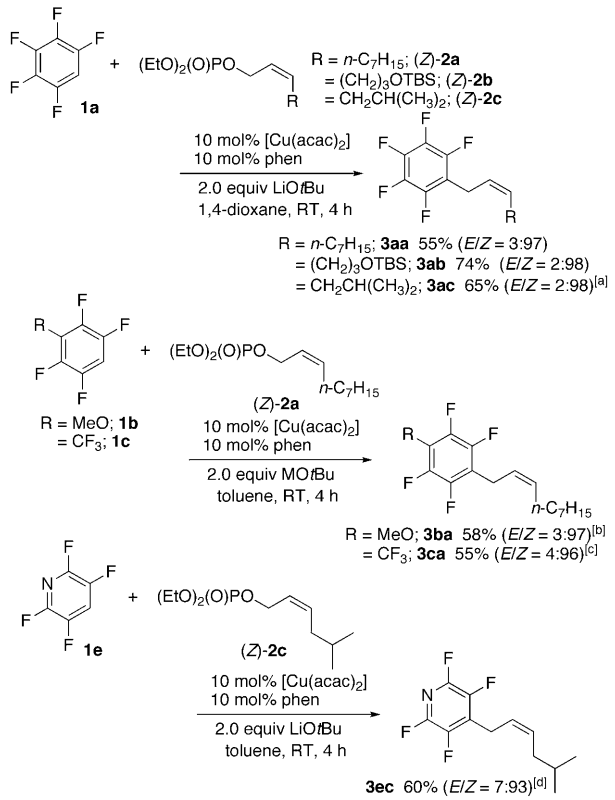
[a] Reaction conditions: $[Cu(acac)_2]$ (0.050 mmol), phen (0.050 mmol), LiO*t*Bu (1.0 mmol), **1a** (0.50 mmol), **2** (0.60 mmol), 1,4-dioxane (3.0 mL), RT, 4 h, N_2. [b] The yields are of isolated products and the *E*/*Z* ratios were determined by ^{1}H NMR spectroscopy. In all cases the linear/branched ratios were >98:2. [c] Contaminated with 2–4% of olefin isomerization product. acac = acetylacetonate, phen = 1,10-phenanthroline, TBS = *tert*-butyldimethylsilyl.



Scheme 2. Copper-catalyzed direct C–H allylation of various fluoroarenes **1** with allyl phosphates **2** performed using the reaction conditions from Table 1. The new C–C bond is illustrated with a bold line. The yields are of the isolated products and *E*/*Z* ratios were determined by ^{1}H NMR spectroscopy. The linear/branched ratios were generally >95:5, except for **3ha**. [a] With NaO*t*Bu and toluene instead of LiO*t*Bu and 1,4-dioxane, respectively. [b] With toluene instead of 1,4-dioxane. [c] With NaO*t*Bu instead of LiO*t*Bu.

(**3ga** and **3ga′**). However, 1,2,4-trifluorobenzene reacted differently than the above tetrafluorobenzenes: 1) it had a comparatively moderate reactivity, 2) allylation occurred exclusively at the C–H bond *ortho* to two fluorine atoms, and 3) a significant amount of the branched isomer was formed (**3ha** and **3ha′**). The moderate reactivity and selectivity of this reaction indicate that the efficiency of the C–H cleavage process is highly dependent upon the acidity of the C–H.[11] Indeed, fluoroarenes bearing less than three fluorine atoms, such as 1,3-difluorobenzene, completely failed to couple with allyl phosphate. The formation of the branched isomer (**3ha′**) might be caused by an alternate catalytically active copper intermediate.[12,13]

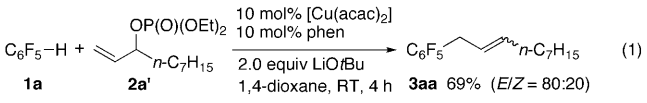
We then turned our attention to the stereospecificity of the reaction when using *Z*-allyl phosphates. Pleasingly, the products were obtained and the stereochemical information of the starting materials was retained (Scheme 3). This phenomenon is significant because the *Z* stereospecificity is not trivial in the arylation of allylic electrophiles, although it is sometimes observed in the reaction using alkyl and hetero-



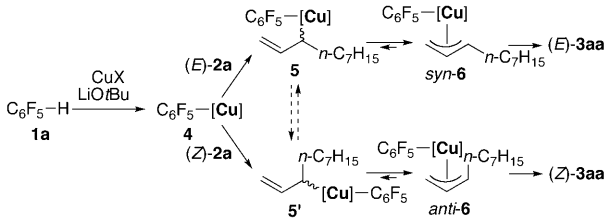
Scheme 3. *Z*-Specific copper-catalyzed C–H allylation of polyfluoroarenes with *Z*-allyl phosphates. [a] Contaminated with a trace amount of the olefin isomerization product. [b] With NaO*t*Bu. Product contaminated with 2% of the olefin isomerization product and 2% of the regioisomer. [c] With LiO*t*Bu. Product contaminated with 1% of the branched isomer. [d] Product contaminated with 6% of the olefin isomerization product.

atom nucleophiles.[14] This unique stereospecificity was general for various polyfluoroarenes. For **1b–e**, the modification of the base or solvent system was necessary for the suppression of undesired olefin isomerization.

Next, to investigate the regiospecificity of the reaction, the regioisomeric allyl phosphate **2a′** was subjected to the standard reaction conditions [Eq. (1)]. The reaction proceeded smoothly to furnish the linear allylated product **3aa** exclusively with moderate *E*/*Z* selectivity,[15] indicating that the π-allyl copper intermediate is involved in the catalytic cycle.



On the basis of these results and literature precedent, we are tempted to suggest the illustrated reaction mechanism (Scheme 4) of the direct, stereospecific allylation of **1a** with (*E*)- and (*Z*)-**2a**. Initial LiO*t*Bu-assisted direct cupration of **1a** gives the pentafluorophenylcopper intermediate **4**.[16] The



Scheme 4. A plausible reaction mechanism. [**Cu**] = copper with appendede ligands such as phen, acac, or $OP(O)(OEt)_2$.

subsequent nucleophilic attack (oxidative addition) on (*E*)- or (*Z*)-**2a** should proceed in an S_N2' manner followed by rapid σ–π conversion to give the π-allyl copper species *syn*-**6** or *anti*-**6**, respectively.[12] Finally, reductive elimination at the less congested carbon center provides the corresponding allylated products (*E*)- or (*Z*)-**3aa**. The σ–π conversion would need to be much faster than rotation between σ-allyl isomers **5** and **5′** for the stereochemical information of the starting allyl phosphate to be transferred into the product.[17] Given that the formation of a π-allyl complex is not regiospecific, the putative **4** might be a diarylcopper species rather than a monoaryl species.[13,18] However, further investigations are essential to clarify the effects of the ancillary ligands including phen, acac, and phosphates, and these are currently underway in our laboratory.

In conclusion, we have demonstrated an efficient copper catalyst system for the direct C–H allylation of polyfluoroarenes with allyl phosphates in a highly stereospecific manner. The process could provide facile access to allylarenes of a strongly electron-deficient nature. Investigations into the application of this method to other arenes and to elucidate the detailed mechanism are in progress.[19]

Experimental Section

Copper-catalyzed direct C–H allylation of pentafluorobenzene (**1a**) with allyl phosphate **2a** (Table 1, entry 1): $[Cu(acac)_2]$ (13.1 mg, 0.050 mmol), 1,10-phenanthroline (9.0 mg, 0.050 mmol), and LiO*t*Bu (80 mg, 1.0 mmol) were placed in a 20 mL two-necked reaction flask, which was filled with nitrogen by using the standard Schlenk technique. 1,4-Dioxane (2.0 mL) was then added to the flask, and the suspension was stirred for 10 min at ambient temperature. Finally, a solution of pentafluorobenzene (**1a**, 84 mg, 0.50 mmol) and allyl phosphate **2a** (175 mg, 0.60 mmol) in 1,4-dioxane (1.0 mL) was added dropwise. The solution was stirred at ambient temperature for 4 h and the resulting mixture was quenched with water. The mixture was extracted with *n*-hexane, and the combined organic layer was dried over sodium sulfate. Concentration of the solution in vacuo and subsequent silica gel column chromatography with *n*-hexane as an eluent gave 1-(pentafluorophenyl)-2-decene (**3aa**, 93 mg, 0.31 mmol, linear/branched 98:2, *E*/*Z* 97:3) in 61% yield.

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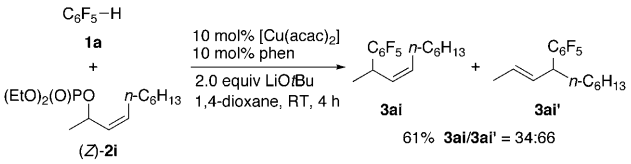

[19] An initial study into the application to 1,3,4-oxadiazole was successful (see the following equation). Attempts to apply the present copper catalytic systems to other acidic azoles such as benzoxazole, benzothiazole, and benzimidazole were unsuccessful (<2% yield by gas chromatography analysis. Further optimization and details will be reported in due course.