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Pd-Catalyzed Dearomative Allylation of Benzyl Phosphates

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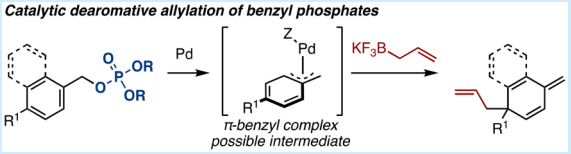
Supporting Information

ABSTRACT: Dearomative C−C bond formation of benzyl phosphates has been developed. In the presence of a palladium/PAr_3 catalyst, benzyl phosphates reacted with allyl borates to generate the allylated product in a dearomative fashion. The resulting dearomatized molecules were successfully derivatized by Simmons−Smith cyclopropanation and oxidation.



Aromatic molecules such as benzene and pyridine are iconic frameworks in the field of organic chemistry and are widely seen in functional organic compounds ranging from pharmaceuticals to organic electronic devices. Several methods to functionalize aromatic molecules are known, such as electrophilic aromatic substitution and metal-catalyzed cross-coupling. In contrast to these aromatic substitution reactions, transformations that achieve C−C or C−heteroatom bond formations with concomitant dearomatization are still underdeveloped (Figure 1).[1] These dearomative reactions are powerful synthetic methods that build valuable alicyclic systems and expand structural diversity. So far, such reactions were achieved mainly by using electron-rich aromatics such as phenols and indoles[2] or electron-poor aromatics such as azines.[3] Electronically unbiased aromatics such as benzenes and naphthalenes are still challenging substrates. Although

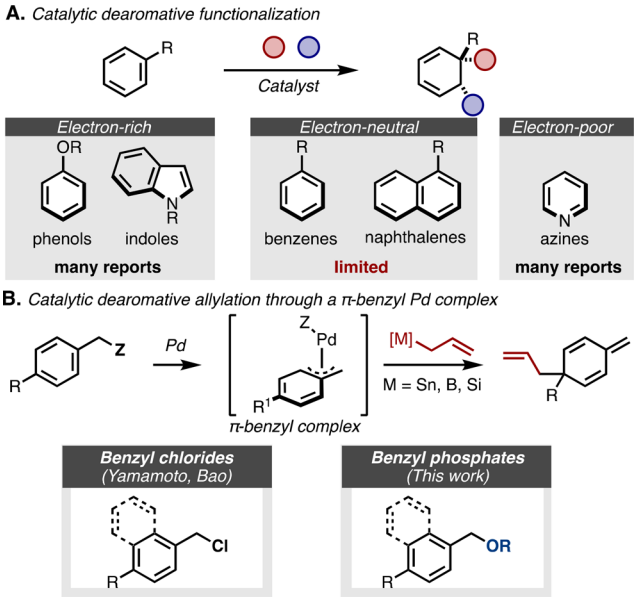


Figure 1. (A) Dearomative functionalization of arenes. (B) Catalytic dearomative allylation of benzene derivatives through a π-benzyl complex intermediate.

methods using π-arene complexes,[4] dihydroxygenase,[5] and arenophiles[6] are known and some of them have been applied to natural products synthesis,[7] they often suffer from reaction efficiency particularly in terms of the stoichiometry of metal reagents as well as starting materials. Furthermore, catalytic methods are currently limited.

With these considerations in mind, we surmised that the metal-catalyzed reaction through a π-benzyl complex intermediate[8] can provide a complementary dearomative method. A π-benzyl complex is relatively easy to generate, and more importantly, the aromatic stabilization of the parent arene is already partially lost in the π-benzyl complex.[8,9] We envisaged that selective addition on a parent arene ring in the π-benzyl complex intermediate could realize an efficient dearomative functionalization. To date, the reactivity of π-benzyl complexes is not fully understood. One example showing specific reactivity of the complex was reported by Yamamoto, where a Pd−π-benzyl complex underwent dearomative substitution in the reaction between benzyl chlorides and allyl stannanes.[10,11] Recently, the Bao group extended this reaction to allow for the use of allyl silanes[11e] and boronic esters[11f] as nucleophilic agents. We envisioned that this chemistry can be extended to more ubiquitous benzylic alcohol derivatives through a benzylic C−O bond cleavage.[12] With facile access from the corresponding aromatic carbonyl compounds, the reaction would be synthetically beneficial. Herein, we report a dearomative allylation of benzyl phosphates with allyl borates by a palladium catalyst.

Our study began by optimizing the reaction between 1-naphthalenemethanol derivatives **1A** and allyl borate **2** as model compounds (Table 1). Delightfully, with $Pd(OAc)_2$, triphenylphosphine worked to produce desired dearomatized product **3A** in moderate yield (Table 1, entry 1). Motivated by this result, we screened a variety of ligands. Electron-donating monodentate phosphine **L1** increased the reaction efficiency to give **3A** quantitatively (Table 1, entry 2). In contrast, the reaction yield decreased when less electron-donating phosphine ligands such as perfluorinated triphenylphosphine

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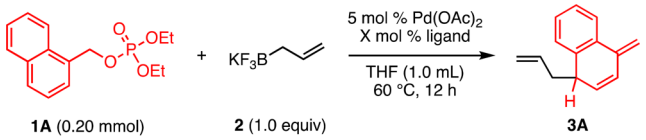
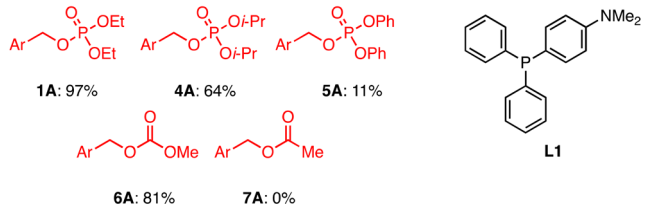
Table 1. Screening of Reaction Conditions[a]



entry	ligand (X mol %)	yield of **3A**[b] (%)	yield of **1A**[b] (%)
1	PPh_3 (20)	63	13
2	**L1** (20)	97	0
3	$P(C_6F_5)_3$ (20)	trace	96
4	$P(OPh)_3$ (20)	53	47
5	IMes·HCl (20)[c]	12	84
6	IPr·HCl (20)[c]	28	72
7	bipy (10)	0	100
8	**L1** (20)[d]	0	100
9	none	0	100

B. ***Effect of leaving group*** (Ar = 1-naphthyl, ligand = **L1**)



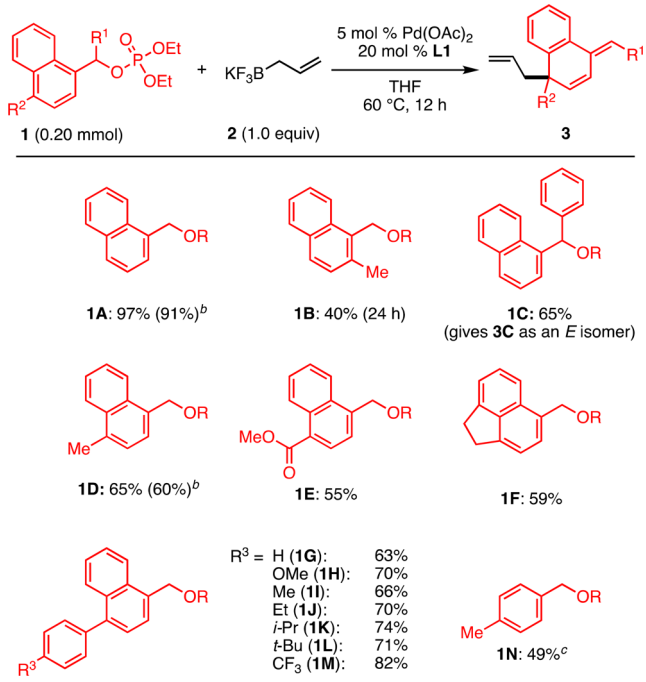
[a]Conditions: **1A** (0.20 mmol), **2** (0.20 mmol), $Pd(OAc)_2$ (5 mol %), ligand, THF (1.0 mL), 60 °C, 12 h. [b]^{1}H NMR yield determined by using CH_2Br_2 as an internal standard. [c]NaO*t*-Bu (20 mol %) was added. [d]Without $Pd(OAc)_2$.

(Table 1, entry 3) and phosphite (Table 1, entry 4) were used. *N*-Heterocyclic carbene ligands also produced **3A**, albeit in lower yields (Table 1, entries 5 and 6). However, nitrogen-based ligand was not productive (Table 1, entry 7). Without either $Pd(OAc)_2$ or ligand, no product was obtained (Table 1, entries 8 and 9). In all experiments using **1A** as the starting material, the undesired coupling product at the benzylic position was not observed. Of note here is that this reaction is conducted using a 1:1 ratio of aromatic substrate to reagent, compared with other dearomatizing methods that often require excess amounts of either the arene component or the reagent.

The effect of the leaving group was examined next (Table 1B). Among phosphates, diethyl phosphate **1A** gave the best result. This reaction also allowed for the use of carbonate as a leaving group (**6A**) although in slightly lower yield. However, ester **7A** unfortunately afforded no dearomatized product **3A**.

Based on these results, we then surveyed the substrate scope (Scheme 1). The reaction yield was determined by ^{1}H NMR analysis because the products were unstable on silica gel.[13,14] A naphthalene with an *ortho* substituent (**1B**) generated product in moderate yield, although the reaction required prolonged reaction time due to steric hindrance. Secondary alcohol derivative **1C** could also be allylated in dearomative fashion, generating **3C** in 65% yield as a single *E* isomer. Delightfully, this protocol allowed for the construction of quaternary carbons starting from C4-substituted benzyl phosphates. For example, **1D** was smoothly allylated under the optimized conditions in 65% yield. Methoxycarbonyl naphthalene **1E** as well as acenaphthene **1F** also underwent the reaction. Several biaryls (**1G**−**1M**) could be dearomatively functionalized in good to moderate yields. Although the reaction efficiency was decreased, simple benzene derivatives **1N** could also be transformed to the dearomatized **3N** in moderate yield. In

Scheme 1. Scope of Benzyl Phosphates for the Dearomative Allylation[a]



[a]Conditions: **1** (0.20 mmol), **2** (0.20 mmol), $Pd(OAc)_2$ (5 mol %), **L1** (20 mol %), THF (1.0 mL), 60 °C, 12 h.^{1}H NMR yield determined by using CH_2Br_2 as an internal standard. [b]1.0 mmol scale. [c]DPEphos (10 mol %), Cs_2CO_3 (3.0 equiv), and **2** (2.0 equiv) were used.

this case, the use of DPEphos instead of **L1** and the addition of Cs_2CO_3 was effective. This protocol was found to be scalable, as seen in the reaction of **1A** and **1D** to produce **3A** and **3D**, respectively, on 1 mmol scale.

As mentioned above, the generated products are unstable and undergo a [1,5]-rearrangement to attain their aromatic form, 4-allyl-1-alkylnaphthalene.[15] This process is significantly accelerated by acid, and therefore, preventing product **3** from aromatizing during subsequent transformations can be challenging. Among a variety of reaction conditions that we tested, we found that Simmons−Smith-type conditions[16] are successful. Treatment of the crude mixture from the dearomative allylation of **1D** with Et_2Zn/CH_2I_2/2,4,6-trichlorophenol afforded cyclopropanated product **7D** in 38% yield over two steps. In this cyclopropanation, the *exo*-methylene group selectively reacted. Furthermore, we found that the same crude mixture of **3D** underwent an unusual ketone formation under the influence of *m*-CPBA, furnishing **8D** in 43% yield over two steps (Scheme 2).[17]

We postulate the reaction mechanism of the dearomative allylation as follows (Scheme 3A):[18] (1) oxidative addition of the benzylic C−O bonds to Pd(0) species **A** generates Pd(II) complex **B**, which is in equilibrium between the σ-allyl and π-allyl species; (2) allyl borate reacts with **B** to give π-allyl π-benzyl Pd(II) complex **C**; (3) **C** generates dearomatized product **3** with the regeneration of Pd(0) to reenter the catalytic cycle. We specifically investigate the reaction of **1A** with (*E*)-crotylborate **9**: we obtained **10** (*linear*) and **11** (*branched*) in a ratio of 40:60, which is in a good accordance with the generation of π-allyl palladium intermediate **C** in the reaction. Although the details of the reaction from **C** are

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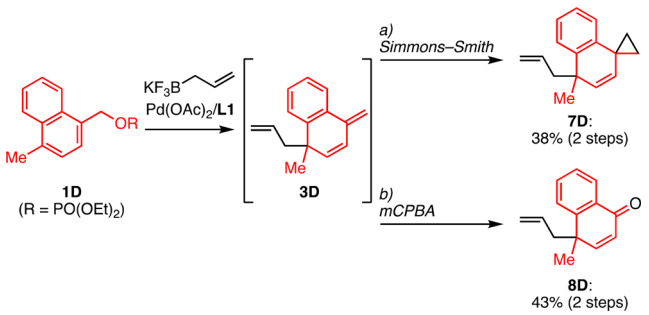
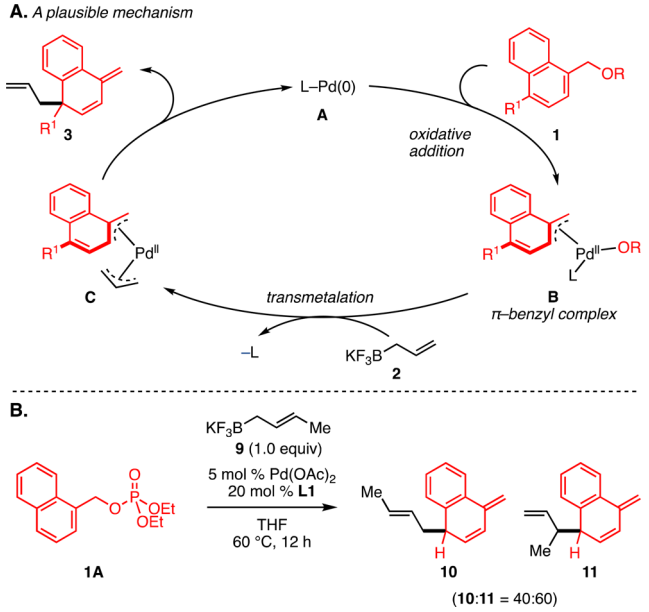
Scheme 2. Derivatization of Dearomatized Product 3D[a]



[a]Conditions: (a) Et_2Zn (1.1 equiv), CH_2I_2 (1.0 equiv), 2,4,6-trichlorophenol (1.0 equiv) in CH_2Cl_2; (b) *m*-CPBA (2.0 equiv), $NaHCO_3$ aq in CH_2Cl_2.

Scheme 3. (A) Plausible Mechanism for the Dearomative Allylation. (B) Dearomative Crotylation of 1A



unclear,[19] we believe that the π-allyl π-benzyl Pd(II) complex **C** may be key for the reaction selectivity because other organoborons such as aryl borates gave benzyl substituted products.[20]

In summary, we have developed a dearomative allylation of benzyl phosphates by a palladium catalyst. This reaction allowed for the use of ubiquitous benzylic alcohols derivatives for the synthesis of substituted alicyclic systems. Elucidation of a more detailed reaction mechanism and expansion of the substrate scope is currently under investigation in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01807.

Detailed experimental procedures, spectral data for all compounds, and ^1H, and ^{13}C, ^{19}F, and ^{31}P NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(13) According to ^{1}H NMR analysis, the products easily undergo rearomatization as a decomposition pathway.

(14) We attempted to isolate and characterize the obtained dearomatized products **3**; however, it was found that the compounds are easily decomposed during purification. Although the isolation of **3A**, **3C**, and **3N** was achieved by Yamamoto and Bao in refs 10 and 11b, we could not reproduce their purification method even by using several kinds of basic alumina. Therefore, we characterized all of the dearomatized compounds **3** after derivatization to stable compounds such as **7** and **8** (see the Supporting Information for details).

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