Dearomative Allylation of Aromatic Cyanohydrins by Palladium Catalysis: Catalyst-Enhanced Site-Selectivity

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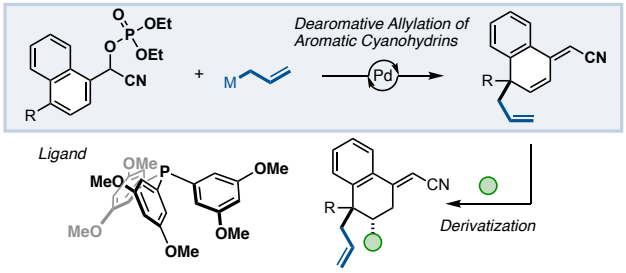
Supporting Information Placeholder

ABSTRACT: A dearomative allylation of aromatic cyanohydrins with allyl borates and allyl stannanes under palladium catalysis was developed. At the initial stage of this study, the dearomative reaction (C4-substitution of the aromatics) was competing with benzyl substitution. To circumvent this issue, the use of palladium and *meta*-disubstituted triarylphosphine as the catalyst in a 1:1 ratio was found to enhance the site-selectivity, furnishing the desired dearomatized products. As the products possess an unsaturated nitrile moiety, further derivatizations of products such as conjugate additions and reductions were achieved.



The chemical transformation of arenes is a fundamental topic in organic synthesis. Many transformations of arenes have been developed, of which electrophilic aromatic substitutions and cross-couplings are recognized as key functionalizations of σ-bonds of aromatic cores.[1] On the other hand, the transformation of ring itself, i.e., the transformation of the π-bonds of arenes such as dearomative reactions is less studied. Nevertheless, this type of reaction can provide high molecular complexity from simple and abundant arenes. With recent developments in metal-catalysis, several dearomatization methods have emerged.[2] For example, the Glorius group recently achieved efficient hydrogenations of arenes to give birth alicyclic compounds with a high stereo-control.[2c–f] For dearomative functionalizations, however there are more limitations than with hydrogenations. For example, the efficiency of the reaction significantly depends on the electronic nature of the arenes. Although electron-rich and electron-poor arenes can mostly be utilized as a limiting agent,[3] electron-neutral arenes are regarded as inactive arenes, usually requiring excess amounts in a reaction.[4,5]Generally, only nitroarenes[6], aryl malonates[7], and aryl iodanes[8] can be utilized for dearomative functionalizations as the limiting reagent.

We recently reported the dearomative allylation of inactive aromatic systems initiated by a catalytic bond cleavage (Figure 1A).[9] So far, we developed the dearomative allylation of benzyl phosphates[9a] as well as aryl bromides[9b] under the influence of a palladium catalyst. Yamamoto and Bao also developed related reactions involving benzyl chlorides.[10] These methods enabled the dearomative functionalization of inactive arenes as a limiting reagent. However, the obtained products were unstable and difficult to derivatize to functionalized alicyclic systems, that restricting further synthetic application. We postulated that this instability was caused by the highly reactive exocyclic olefin of the products. To achieve the dearomative synthesis of multi-functionalized alicyclic molecules, we selected aromatic cyanohydrin phosphates as the substrate,[11] which possess a cyano group at the benzyl position (Figure 1B). These were readily prepared from the corresponding aldehydes in one step.[12] More importantly, since the dearomatized products have an α,β-unsaturated cyano moiety, they are expected to be functionalized through a conjugate addition. With this application in mind, we herein report the development of dearomative allylation of aromatic cyanohydrins by a palladium catalyst.

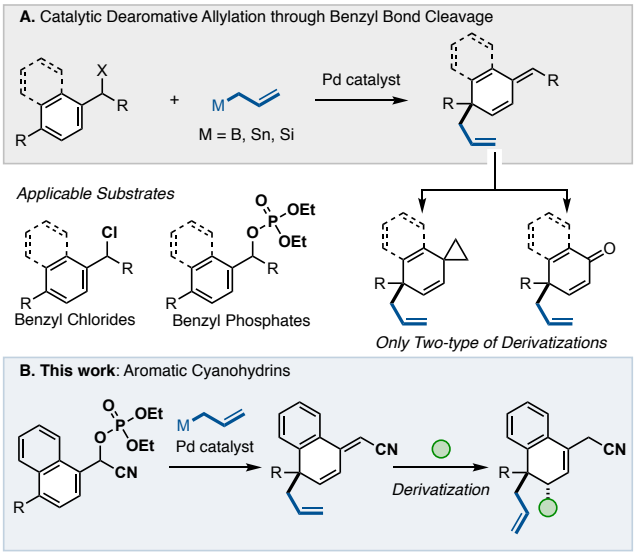
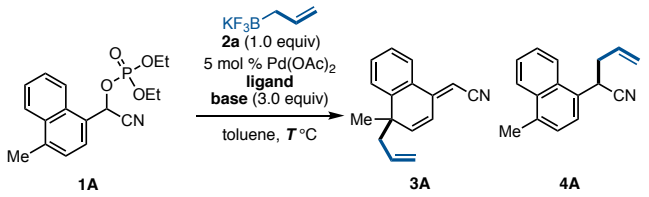


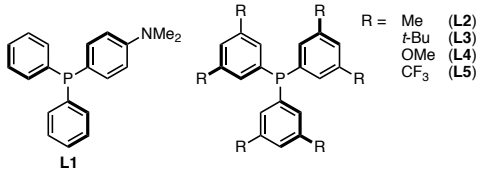
Figure 1. (**A**) Catalytic dearomative allylation. (**B**) Dearomative allylation of aromatic cyanohydrins

We initiated this study by investigating the reaction conditions using naphthalene cyanohydrin **1A** with allyl trifluoroborate **2a** (Table 1). As a first trial, our previous reaction conditions for dearomative allylation of benzyl phosphates were examined (Table 1, entry 1).[9a] However, the reactivity of cyanohydrins and simple benzyl phosphates are rather different for this catalytic system, generating only the undesired benzyl-substituted product **4A** in 83% yield. We hypothesized that this site-selectivity occurred due to the highly electrophilic nature of the α-cyano moiety leading to undesired benzyl substitution. Thus, the reaction temperature was decreased from 60 °C to room temperature. To our delight, the dearomative reaction proceeded to give the desired product (dearomative allylation product) **3A** in 40% yield, along with the undesired **4A** in a ratio of 1:1 (Table 1, entry 2). Lowering the reaction temperature to 4 °C resulted in no reaction (Table 1, entry 3). Interestingly, when the ratio of metal/ligand was changed, decreasing the amount of ligand improved this site-selectivity (Table 1, entry 2 vs. entries 4 and 5). Next, the effect of the ligand was investigated. Simple PPh_3 decreased the yield of **3A** and **4A** while retaining the site-selectivity (Table 1, entry 6). When using *o*-, *m*-, and *p*-tolyl phosphines, it was found that *m*-tolyl phosphine was effective (Table 1, entries 7–9). Encouraged by the effect of *meta*-substituents, we synthesized and evaluated several *m*-disubstituted triarylphosphines (Table 1, entries 10–13). As a result, electron-rich *m*-disubstituted triarylphosphines were found to be favorable for both reaction yield and site-selectivity, out of which *m*-dimethoxyphenyl phosphine **L4** gave the best result (Table 1, entry 12). Delightfully, the addition of Cs_2CO_3 as a base improved the reaction efficiency, furnishing the product **3A** in 70% yield with high site-selectivity (Table 1, entry 14).

Table 1. Screening of Reaction Conditions[a]



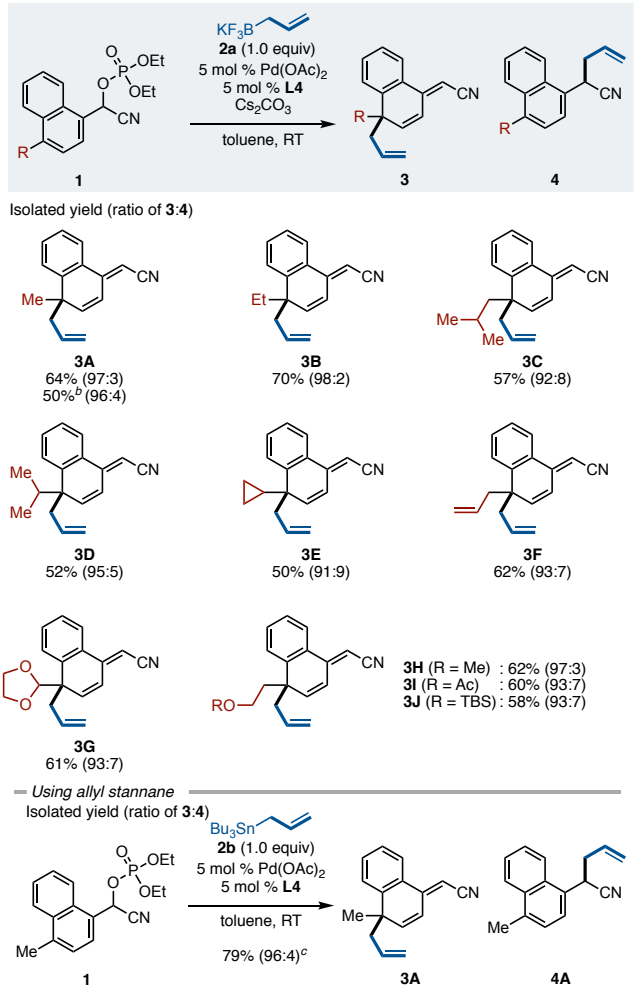
entry	ligand (mol %)	base	*T*/°C	3A+4A/%	3A:4A
1	**L1** (20)	–	60	83	0:100
2	**L1** (20)	–	RT	82	49:51
3	**L1** (20)	–	4	0	–
4	**L1** (10)	–	RT	61	74:26
5	**L1** (5)	–	RT	53	87:13
6	PPh_3 (5)	–	RT	36	86:14
7	P(*o*-tol)$_3$ (5)	–	RT	3	–
8	P(*m*-tol)$_3$ (5)	–	RT	46	91:9
9	P(*p*-tol)$_3$ (5)	–	RT	33	88:12
10	**L2** (5)	–	RT	35	91:9
11	**L3** (5)	–	RT	40	91:9
12	**L4** (5)	–	RT	44	95:5
13	**L5** (5)	–	RT	0	–
14	**L4** (5)	Cs_2CO_3	RT	70	97:3



[a] Conditions: **1A** (0.20 mmol), **2** (0.20 mmol), $Pd(OAc)_2$ (5 mol %), ligand, base (3.0 equiv), toluene (1.0 mL), 12 h. [b] NMR yield.

With the optimized conditions in hand, we evaluated the substrate scope of the present reactions (Scheme 1). The reaction was applicable to C4-substituted naphthalenes. Several C4-alkylated naphthalene cyanohydrins underwent the reaction, giving the corresponding products **3** in moderate to good yields with high site-selectivity (**3A**–**3C**). A sterically demanding isopropyl group was also compatible in this reaction (**3D**). A strained alkyl group such as cyclopropyl was tolerated to give **3E** in moderate yield. Reactive functional groups such as acetal (**3G**), ester (**3I**), and silyloxy group (**3J**) were intact under the reaction conditions. Furthermore, allyl stannane was found to be applicable as the allylating agent in the absence of base, furnishing **3A** in good yield with high site-selectivity. It is noteworthy that these dearomatized products were reasonably stable, not decomposing during silica-gel column chromatography.

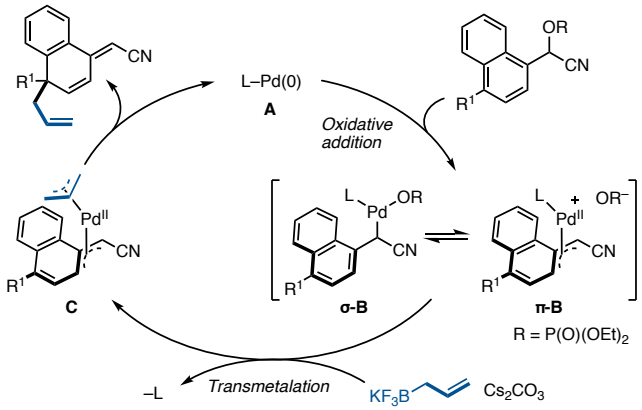
Scheme 1. Substrate Scope [a]



[a] Conditions. **1** (0.20 mmol), **2a** (0.20 mmol), $Pd(OAc)_2$ (5 mol %), **L4** (5 mol %), Cs_2CO_3 (3.0 equiv), toluene (1.0 mL), RT, 12 h. [b] 1.0 mmol scale. [b] Determined by ^{1}H NMR.

A possible reaction mechanism is outlined in Scheme 2.[13] First oxidative addition of C–O bonds to palladium(0) species gives benzyl-palladium **B**, which is in equilibrium between σ- and π-benzyl species. To this species, allyl borates undergo transmetalation, generating allyl-palladium-benzyl intermediate **C**. Finally, reductive elimination forms the C–C bond at the remote-site, releasing the dearomatized products with regeneration of the active palladium(0) species.[14]

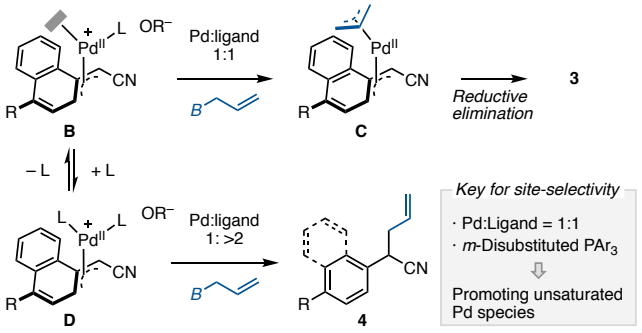
Scheme 2. Proposed Mechanism.



At this stage, we speculate that the observed catalyst-enhanced site-selectivity may be triggered by the generation of coordinatively unsaturated palladium species **B** (Scheme 3). The reaction conditions using a 1:1 ratio of palladium and ligand would generate a coordinatively unsaturated palladium intermediate. Thus, the allyl boron species can undergo transmetalation to give the allyl-Pd-benzyl intermediate, followed by reductive elimination at the C4 position to furnish the dearomatized product.[14] In contrast, when palladium and ligand were used in a ratio of 1:2 or more, coordinatively saturated species **D** would be generated as the major catalytic intermediate. Probably due to the highly electrophilic nature of the cyano-bearing benzyl carbon, the allyl borons likely prefers external attack onto **D**, giving the benzyl-substituted compound as the major product.

meta-Disubstituted triarylphosphines likely enforce the generation of coordinatively unsaturated palladium **B** by steric repulsion. According to Tsuji's work, *meta*-disubstituted triarylphosphines have a bowl-shaped structure, accelerating the dissociation of other ligands but providing reaction space around the metal center.[15] In line with these reports, the use of *meta*-disubstituted triarylphosphines would support the generation of a coordinatively unsaturated palladium species in this catalytic system.

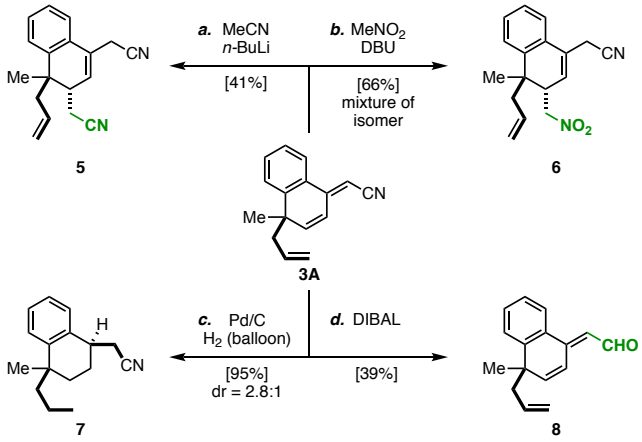
Scheme 3. Possible Role of Catalyst for Site-Selectivity.



Although *o*-substituted triarylphosphines are also expected to give coordinatively unsaturated palladiums, they cannot provide enough reaction space around the metal center, blocking the desired transmetalation of allyl borons.[16]

Finally, we performed several transformations of dearomatized product **3A** (Scheme 4). The α,β-unsaturated cyano moiety is expected to be functionalized through several nucleophilic additions. Although we expected that 1,4-addition would occur when using carbon nucleophiles, the reaction using lithioacetonitrile afforded 1,6-adduct **5** instead. A similar regioselectivity was observed when nitromethane was reacted with **3A** in the presence of DBU, furnishing **6**. This regioselectivity is likely due to the steric repulsion of the δ,γ-unsaturated olefin (disubstituted) vs the α,β-unsaturated olefin (trisubstituted) to circumvent the expected 1,4-addition. Furthermore, we succeeded in the reductive derivatization of **3A** through global hydrogenation, furnishing substituted tetralin **7**. Treatment of **3A** with DIBAL was also successful to deliver enal **8**.

Scheme 4. Derivatization of 3A.



In summary, we developed a dearomative allylation of aromatic cyanohydrins by a palladium catalyst. The combination of palladium and *m*-disubstituted triarylphosphines enhanced site-selectivity, furnishing dearomatized molecules. Importantly, the dearomatized products were able to be derivatized to a variety of substituted alicyclic systems. We believe that the present work would provide a useful synthetic entry to alicyclic molecules and lead to an in-depth understanding of the mechanism of related reactions. Further studies to expand the substrate generality and elucidate the mechanism are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for compounds including ^{1}H, ^{13}C, ^{31}P NMR spectra (PDF)

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Notes

No competing financial interests have been declared.

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(16) See the Supporting Information for details.