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Palladium-Catalyzed Dehydrative Cross-Coupling of Allylic Alcohols and *N*-Heterocycles Promoted by a Bicyclic Bridgehead Phosphoramidite Ligand and an Acid Additive

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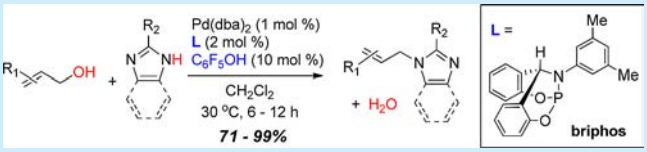
Supporting Information

ABSTRACT: A mild and efficient dehydrative cross-coupling reaction between allylic alcohols and *N*-heterocycles using palladium catalysis is reported. A bicyclic bridgehead phosphoramidite (briphos) ligand together with $Pd(dba)_2$ is a highly efficient catalyst, and an acid additive involved in the rate-determining step promotes the catalytic cycle. The coupling reaction of allylic alcohols with *N*-heterocycles including imidazoles, benzimidazoles, and triazole proceeds under mild reaction conditions with high yields using Pd/briphos and pentafluorophenol.



In recent years, dehydrative cross-coupling reactions between alcohols and nucleophiles have emerged as atom-economical and environmentally benign processes because they eliminate preactivation of the hydroxyl group and generate water as the only byproduct.[1] In this respect, Pd-catalyzed allylic substitution using allylic alcohols has been a topic of interest.[2] In 2002, Ozawa first reported direct coupling reactions of allylic alcohols with aniline or 1,3-dicarbonyl compounds using (π-allyl)palladium complexes without Lewis acid activating agents.[3] Later, the reaction scope of the Pd-catalyzed dehydrative allylic substitution was expanded to *C*-alkylation of indoles by Tamaru[4] and *N*-alkylation of aliphatic amines and electron-poor *N*-heterocycles by Beller.[5]

In this context, two methods for activation of allylic alcohols were proposed using (1) π-acidic phosphorus ligands[3,6,7] and (2) hydrogen bond donors[8,9] (Figure 1a). Ozawa[3] and Ikariya[7] reported favorable ligand effects with sp^2-hybridized phosphorus ligands and triphenyl phosphite, respectively, while Reek[8] reported hydrogen-bond-assisted activation with a combination of functionalized phosphoramidite ligands and urea additives. However, the substrate scope of Pd-catalyzed dehydrate allylic substitution is still quite limited as compared with the Tsuji–Trost allylic substitution,[10] a well-established synthetic proce-

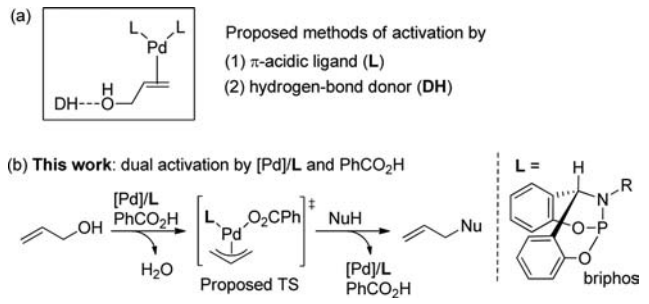
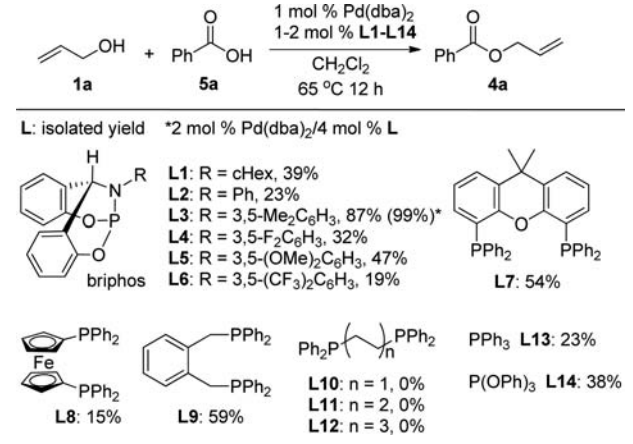
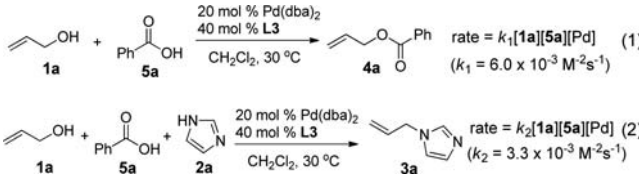


Figure 1. (a) Proposed activation methods for Pd-catalyzed dehydrative coupling of allyl alcohol and (b) a dehydrative cross-coupling of allyl alcohol and nucleophile (NuH) via a dual activation with [Pd]/**L** and $PhCO_2H$.

Scheme 1. A Survey of Ligand Effect on the Pd-Catalyzed Dehydrative Coupling of Allyl Alcohol (1a) with Benzoic Acid (5a)





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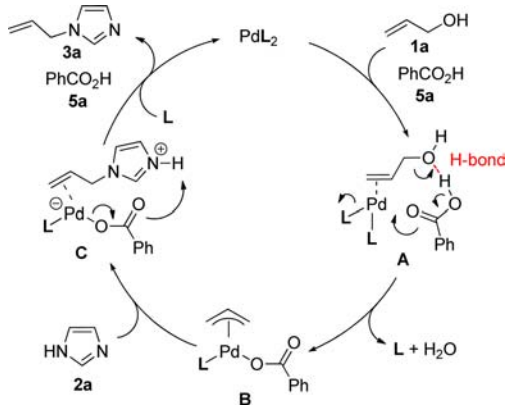


Figure 2. A proposed catalytic cycle on the basis of kinetic data.

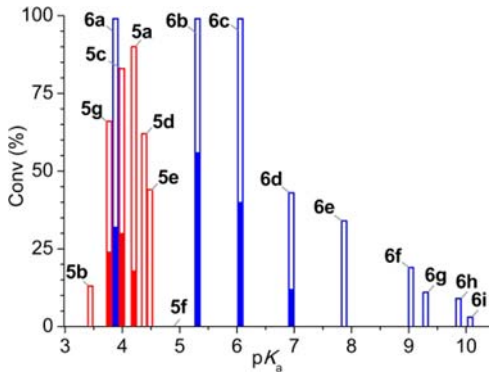


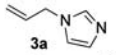
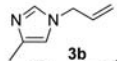
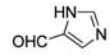
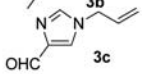
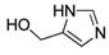
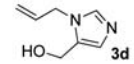
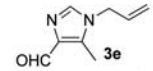
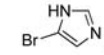
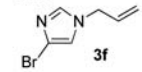
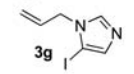
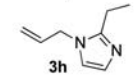
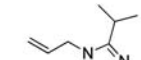
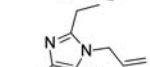
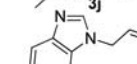
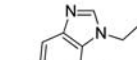
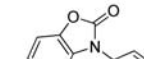
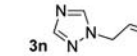
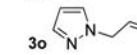
Figure 3. Additive effects with respect to relative acidity (**5a**: $PhCO_2H$, **5b**: *p*-$NO_2C_6H_4CO_2H$, **5c**: *p*-$BrC_6H_4CO_2H$, **5d**: *p*-$EtC_6H_4CO_2H$, **5e**: *p*-$EtOC_6H_4CO_2H$, **5f**: *p*-$NMe_2C_6H_4CO_2H$, **5g**: CH_3CO_2H, **6a**: 2,4-$(NO_2)_2C_6H_3OH$, **6b**: C_6F_5OH, **6c**: 2,4,6-$Cl_3C_6H_2OH$, **6d**: *p*-$NO_2C_6H_4OH$, **6e**: *p*-CNC_6H_4OH, **6f**: *p*-BrC_6H_4OH, **6g**: *p*-$CF_3C_6H_4OH$, **6h**: PhOH, and **6i**: *p*-MeC_6H_4OH). Additives were either 100 mol % (open bar) or 10 mol % (filled bar).

dure for the construction of C−C, C−N, C−O, and C−S bonds using activated allylic compounds such as allyl acetates or allyl bromides. Thus, a highly efficient activation method is required to expand the reaction scope of Pd-catalyzed dehydrative allylic substitution.

The favorable ligand effect for the activation of allylic alcohols caught our attention as we have recently developed a new type of tunable π-acceptor ligands, bicyclic bridgehead phosphoramidites (briphos) (Figure 1b).[11] We have shown that the geometrical constraints in briphos significantly enhance the ligand's π-acceptor ability and this ligand is highly efficient for Rh-catalyzed conjugate addition of aryl boronic acids.[11] After the investigation of Pd-catalyzed dehydrative coupling of allylic alcohols with tunable π-acceptor ligands (briphos), we report here that Pd(0)/briphos is a highly reactive catalyst for activation of allylic alcohols. Moreover, our kinetic experiments reveal that an acid additive, benzoic acid, is involved in the transition state of the rate-determining step (Figure 1b). As a result, the Pd-catalyzed dehydrate cross-coupling of allylic alcohols and *N*-heterocycles can be achieved under mild reaction conditions via a dual effect of a briphos ligand and an acid additive.

The imidazole nucleus is one of the versatile heterocyclic structures used for making many biologically active compounds.[12] Despite continuing interest in the preparation of imidazole derivatives, *N*-allylation of imidazoles still rely on base-mediated alkylation with allyl halides, which produces a

Table 1. Pd-Catalyzed Dehydrative Cross-Coupling of Allyl Alcohol (1a) with Various *N*-Heterocycles[a]

entry	*N*-heterocycle	major product[b]	yield (%)[c]	product ratio[d]
1			96	-
2[e]			97	55:45
3			97	92:8
4			90	7:3
5			94	91:9
6			93	77:23
7[e]			78	95:5
8[e]			98	-
9[e]			97	-
10[e]			71	89:11
11			97	-
12			95	1:1
13[e]			92	-
14			97	-
15			94	-

[a]Conditions: **1a** (1.1 mmol), **2** (0.7 mmol), $Pd(dba)_2$ (1.0 mol %), **L3** (2.0 mol %), and **6b** (10 mol %) were stirred in CH_2Cl_2 (0.7 mL) at 30 °C for 6 h. [b]The allylation occurred at the other N atom in the minor isomer. [c]Yield of isolated product. [d]Determined by ^{1}H NMR spectra of crude mixture. [e]12 h.

stoichiometric amount of salts as byproduct.[13] In order to develop a greener process, we first investigated Pd-catalyzed dehydrative coupling of imidazole and allyl alcohol. In our initial attempts, $Pd(dba)_2$/briphos **L3** (Scheme 1) was found to be inefficient for the direct coupling of imidazole **2a** and allyl alcohol **1a** at 30 °C, whereas $Pd(dba)_2$/**L3** provided the allylated imidazole **3a** with allyl benzoate **4a** in quantitative yield. Remarkably, the addition of 1 equiv of benzoic acid **5a** promoted the dehydrative coupling between imidazole **2a** and allyl alcohol **1a** to provide the product **3a** in 96% yield.

We then performed kinetic experiments to verify the role of the acid additive and the mechanism of the activation of the allyl alcohol. The initial rate of the Pd-catalyzed coupling between allyl alcohol **1a** and benzoic acid **5a** showed a first-order

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Table 2. Pd-Catalyzed Dehydrative Cross-Coupling of Different Allylic Alcohols with Imidazole (2a)[a]

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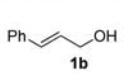
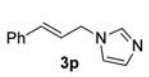
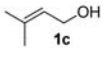
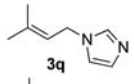
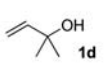
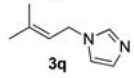
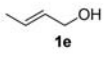
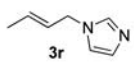
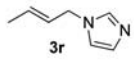
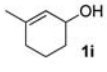
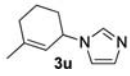
1	 1b	 3p / 3p'	96	>50:1
2	 1c	 3q / 3q'	90	>50:1
3	 1d	 3q / 3q'	99	>50:1
4	 1e	 3r / 3r'	98	83:17
5	 1f	 3r / 3r'	99	88:12
6	 1g	 3s	98	-
7	 1h	 3t	87	-
8	 1i	 3u / 3u'	75	>50:1

[a]Conditions: **1** (1.1 mmol), **2a** (0.7 mmol), $Pd(dba)_2$ (1.0 mol %), **L3** (2.0 mol %), and **6b** (10 mol %) were stirred in CH_2Cl_2 (0.7 mL) at 30 °C for 6 h. [b]Yield of isolated product. [c]Determined by ^1H NMR spectra of crude mixture.

dependence on the concentrations of Pd/**L**, **1a**, and **5a** (eq 1). Accordingly, both a Pd catalyst and benzoic acid are required for the activation of the allyl alcohol, supporting the role of a π-acidic ligand and hydrogen bond donor. Remarkably, the rate for the coupling of allyl alcohol and imidazole in the presence of benzoic acid (eq 2) showed the same rate equation found in eq 1, indicating that the rate-determining step for the both reactions is the activation of allyl alcohol **1a**.

On the basis of the measured rate equations, we can propose a catalytic cycle for the dehydrative cross-coupling of allyl alcohol and imidazole in the presence of benzoic acid (Figure 2). Assembly of Pd/L_2, allyl alcohol **1a**, and benzoic acid **5a** leads to the formation of π-allyl palladium complex **B**,[14] which is the rate-determining step. As shown in structure **A**, there is an intermolecular hydrogen bonding between benzoic acid **5a** and allyl alcohol **1a**. The complex **B** then reacts with imidazole **3a** to give allyl imidazole **3a**.

Because the activation of allyl alcohol, the rate-determining step, is dependent on the Pd catalyst, allyl alcohol, and benzoic acid, we systematically explored the effects of ligands and acid additives. We first investigated Pd-catalyzed dehydrative coupling of allyl alcohol **2a** and benzoic acid **5a** using various ligands (Scheme 1). In our reaction conditions, 1.0 mol % of $Pd_2(dba)_2$ and 2.0 mol % of ligands (or 1.0 mol % of bidentate ligands) were added to a solution of substrates in toluene. When the reaction was heated at 65 °C for 12 h, commercially available mono- and bidentate aryl substituted phosphorus ligands (**L7**−**L13**) only gave allyl benzoate **4a** in low to moderate (0−59%) yields. Moreover, a π-acceptor ligand, $P(OPh)_3$ (**L14**), also gave the product in 38% yield. Indeed, to the best of our knowledge no efficient catalytic systems have been reported for the dehydrative coupling between benzoic acid **5a** and allyl alcohol **1a**. Remarkably, when a series of briphos ligands (**L1**−**L6**), showing a range of π-acceptor ability with respect to the *N*-substituents, were tested, improved yields were obtained (as high as 87%) with **L3**. We have previously shown that briphos **L3** is the most efficient ligand for Rh-catalyzed conjugate addition of aryl boronic acids to α,β-unsaturated *N*-tosyl ketimines.[11b] With highly efficient briphos **L3**, we further optimized the reaction conditions to find $Pd(dba)_2$ and CH_2Cl_2 as the best Pd source and solvent, respectively (Supporting Information).

The effect of acid additives is then explored. Moreover, we tested the possibility of using catalytic amounts of acid additive because it can be regenerated after completion of the catalytic cycle. Figure 3 shows our systematic investigation of the additive effect using benzoic acid and phenol derivatives over a range of pK_a values. When 1 equiv of benzoic acid derivatives (**5a**−**f**) and acetic acid (**5g**) with pK_a values of 3.44−4.98 were used, an interesting bell-shaped distribution of product yield was obtained with the highest value of 87% by benzoic acid **5a** (pK_a = 4.2). However, the use of 0.1 equiv of benzoic acid **5a** only resulted in a 30% yield, indicating that the recycling of **5a** was inefficient. We next used phenol derivatives (**6a**−**i**) with a much wider pK_a range available (from 4.1 to 10.2). When 1 equiv of phenol derivatives was used, an increase of yields was observed as a decrease of pK_a values of phenol derivatives. All acidic phenol derivatives (**6a**−**c**) with pK_a values of less than 6.2 gave the product with 99% yields. Additionally, among phenol additives, pentafluorophenol **6b** gave the highest yield (56%) when 0.1 equiv was used.

With optimized ligand **L3** and additive **6b**, we conducted a survey on *N*-allylation of *N*-heterocycles as summarized in Table 1. Indeed, in the presence of 1 mol % $Pd(dba)_2$, 2 mol % **L3**, and 10 mol % **6b**, all reactions went to completion at 30 °C in CH_2Cl_2 within 24 h with high yields of 71−98%. For imidazole derivatives (entries 1−10), substitutions at the C2, C4, or C5 position or functional groups such as alcohol, aldehyde, and halides are compatible for the Pd/**L3**-catalyzed dehydrative coupling reaction. In the case of imidazoles with different substitution sites, *N*-allylated products were obtained in various ratios, which corresponds to the base-mediated *N*-allylation with allyl bromides (Supporting Information). Thus, the regioselectivity of dehydrative *N*-allylation appears to be controlled by the nucleophilicity of *N*-nucleophiles. Other *N*-heterocycles including benzimidazoles, 1,2-imidazole, and 1,2,4-triazole were successfully used for dehydrative *N*-allylation (entries 11−15). Thus, the dehydrative coupling reaction catalyzed by Pd/**L3** and pentafluorophenol **6b** can be an efficient protocol for *N*-allylation of various *N*-heterocycles.

We next investigated the dehydrative coupling of imidazole with various allylic alcohols (Table 2). Under our optimum conditions as in Table 1, all desired products were obtained with high yields of 75−99%. Use of cinnamyl alcohol gave the product with 96% (entry 1). For two regioisomeric allylic alcohols that provide the same η^3-π allyl Pd species (entries 3−6), the same ratio of linear/branch products was obtained, which agrees with the results of previous studies that the electrophilicity between the C1 and C3 position of η^3-π allyl Pd species determines the product selectivity.[4c,7a] Moreover, mono-, di-, and trisubstituted alkene moieties are all compatible for the Pd/briphos/pentafluorophenyl catalyzed dehydrative coupling reaction.

In summary, we have developed a dual activation method of using a π-acceptor ligand, briphos **L3**, and pentafluorophenol for the Pd-catalyzed dehydrative coupling of allyl alcohols and *N*-heterocycles including imidazoles, benzimidazoles, and triazole. The kinetic data indicated that the activation of the allyl alcohol is

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the rate-determining step and the rate is dependent on the concentrations of the Pd catalyst, allyl alcohol, and acid additive. Thus, Pd/briphos and pentafluorophenol significantly facilitate the coupling reaction to provide *N*-allylated heterocycles under mild conditions (30 °C) with high yields (71−99%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00001.

Experimental procedures and spectroscopic details (PDF)

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Notes

The authors declare no competing financial interest.

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