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Direct use of allylic alcohols and allylic amines in Palladium-catalyzed allylic amination

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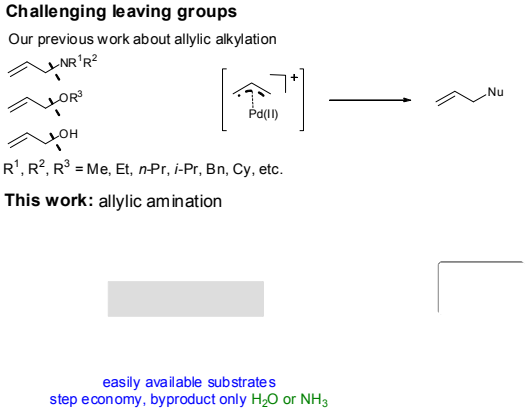
Allylic alcohols and allylic amines were directly utilized in a Pd-catalyzed hydrogen-bond-activated allylic amination under mild reaction conditions in the absence of any additives. The cooperative action of a Pd-catalyst and a hydrogen-bonding solvent is most likely responsible for its high reactivity. The catalytic system is compatible with a variety of functional groups and can be used to prepare a wide range of linear allylic amines in good to excellent yields. Furthermore, this methodology can be easily applied to the one-step synthesis of two drugs, cinnarizine and naftifine, on a gram scale.

Allyl amines are highly important building blocks for various bioactive compounds and key intermediates for the total synthesis of natural products.[1] Palladium-catalyzed allylic substitution with nitrogen nucleophiles is one of the most powerful and reliable methods for the synthesis of allylamines.[2] One of the most common features of this transformation is that substrates with a wide range of good leaving groups (acetates, carbonates, etc.) can be utilized to form η^3-allylpalladium complexes. Despite significant advances in palladium-catalyzed allylic amination through the pre-activation of the parent allylic alcohol,[3] the direct use of the accessible allylic alcohols in this area remains a challenge. It's worth noting that the use of allylic alcohols as substrates would avoid the additional steps for the preparation of the corresponding activated substrates and the generation of more than stoichiometric amounts of unwanted chemical products in both pre-activation and amination steps. Thus the development of an efficient catalytic system that enables the direct amination of allylic alcohols is gaining increasing attention in terms of atom-economy[4] and environmental concerns. Although much progress has been made towards the development of catalytic systems to facilitate the aforementioned reaction,[5] most of these methods require activators,[6] special ligands,[7] or heterogeneous conditions.[7d,7h-i] Therefore, a simple and convenient method for the direct use of allylic alcohols is highly desired. In such reactions, only the desired allylamine product, together with water as a waste product, are produced (Scheme 1).



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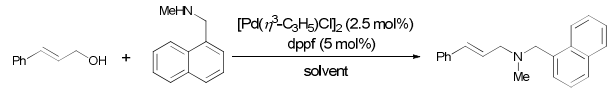
bonding solvent under homogeneous conditions, in the absence of any additives (Scheme 1).

Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

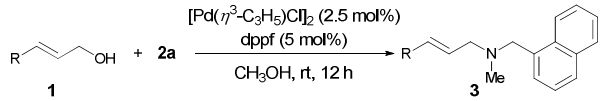
Entry	Solvent	pK_a[b]	*t* (h)	Yield (%)[c]
1	MeOH	15.5	12	96
2	EtOH	15.9	12	84
3	*n*-PrOH	16.1	12	71
4	*i*-PrOH	17.1	12	67
5[d]	*t*-BuOH	18.0	12	52
6	CF_3CH_2OH	12.4	24	trace
7	Toluene	--	24	NR
8	THF	--	24	NR
9[e]	MeOH	15.5	12	79
10[f]	MeOH	15.5	12	96

[a] Reaction of cinnamyl alcohol (0.50 mmol, 1.0 equiv) with 1-methyl-aminomethyl naphthalene (0.75 mmol, 1.5 equiv) was performed using dppf (5.0 mol%) and [Pd(η^3-allyl)Cl]$_2$ (2.5 mol%) as a catalytic system in solvent (2 mL) at rt. [b] See ref 11. [c] Yield of isolated product. [d] 30 °C instead of rt. [e] 0.50 mmol **2a**. [f] 1.0 mmol **2a**. The ligand was 1,1′-bis(diphenyl phosphino) ferrocene (dppf), NR = no reaction.

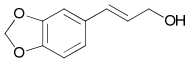
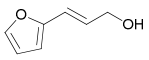
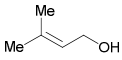
We first carried out the reaction using cinnamyl alcohol (**1a**) as the substrate, 1-methyl-aminomethyl naphthalene (**2a**) as the nucleophile, with a [Pd(η^3-allyl)Cl]$_2$/dppf catalytic system (Table 1). The effects of solvent on the reaction were first explored. When a protic solvent such as MeOH, EtOH, *n*-PrOH, *i*-PrOH, or *t*-BuOH was used, the reaction proceeded smoothly (entries 1-5). The use of CF_3CH_2OH as a solvent was also explored, as it has a beneficial effect on the ionization of the leaving group. The results suggested that our catalytic system was more effective in the absence of acid activators (entry 6). When aprotic solvents (toluene and THF) were used, the reaction was unsuccessful (entries 7 and 8). The above results together with our previous theoretical calculations indicated that hydrogen bond activation of the substrates with alcohol solvents plays a crucial role in the generation of the π-allylpalladium species.[10a] The amount of amine was also screened (entries 9 and 10) and the optimal reaction conditions were found to be: cinnamyl alcohol/amine = 1:1.5, and 2.5 mol% [Pd(η^3-allyl)Cl]$_2$/dppf as a catalyst in methanol at room temperature for 12 h.

Under the optimized reaction conditions, a variety of allylic alcohols were first examined (Table 2). Allylic alcohols substituted with arenes bearing methoxyl or fluorine groups at the *ortho*-, *meta*-, or *para*-position furnished their respective products (**3b**-**3f**) smoothly in high yields (entries 2-6). Cinnamyl alcohol incorporating arenes with electron-withdrawing substituents at the *para*-position were also amenable to the reaction conditions, affording the desired products (**3g**) in 84% yield (entry 7). A substrate bearing a 3,4-methylenedioxy group on the aryl ring could be transformed in high yield (entry 8). Additionally, the reactions of naphthyl- and furyl-substituted allyl alcohols were successfully employed to deliver their desired products (entries 9 and 10). Notably, the branched allylic alcohol was efficiently converted into a linear product in excellent yield (entry 11). Furthermore, the simple prop-2-en-1-ol also reacted to form product **3l** in good yield with high reactivity (entry 12). Finally, the non-aryl substituted allylic alcohols were also explored (entries 13 and 14). The desired products were obtained in 78% and 51% yields respectively, with a small amount of branched products at 50 °C.

Table 2 Substrate scope of allylic alcohols[a]



1 3

Entry	Allylic alcohols	1	Product 3	Yield (%)[b]
1	Ph, OH	**1a**	**3a**	96
2	2-MeOC$_6$H$_4$, OH	**1b**	**3b**	96
3	3-MeOC$_6$H$_4$, OH	**1c**	**3c**	83
4	4-MeOC$_6$H$_4$, OH	**1d**	**3d**	92
5	3-FC$_6$H$_4$, OH	**1e**	**3e**	91
6	4-FC$_6$H$_4$, OH	**1f**	**3f**	88
7[c]	4-CF$_3$C$_6$H$_4$, OH	**1g**	**3g**	84
8		**1h**	**3h**	85
9	2-naphtyl, OH	**1i**	**3i**	92
10[c]		**1j**	**3j**	82
11		**1k**	**3k**	95
12		**1l**	**3l**	84
13[c]	Me, OH	**1m**	**3m**	78 (*E*:*Z* = 5:1)
14[d]		**1n**	**3n**	51 (l:b = 8:1)

[a] Allylic alcohols (0.50 mmol, 1.0 equiv), **2a** (0.75 mmol, 1.5 equiv). [b] Isolated yields. [c] **1m** (1.0 mmol, 2.0 equiv), **2a** (0.50 mmol, 1.0 equiv), [Pd(η^3-allyl)Cl]$_2$ (5.0 mol%) and dppf (10.0 mol%) at 50 °C for 24 h. [d] **1n** (1.0 mmol, 2.0 equiv), **2a** (0.50 mmol, 1.0 equiv) at 50 °C for 24 h.

We then turned our attention to investigating the scope of the amination with regard to the amine component (Table 3). A range of primary and secondary amines participated in the allylic amination to give the desired products in moderate to high yields. Specifically, primary amines such as benzylamine and diphenylmethanamine were amenable to the allylic

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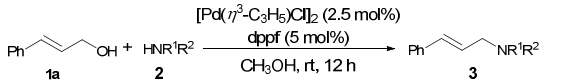
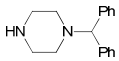
amination, affording the desired products in moderate yields and with less diallylation by-products (entries 1 and 2). Cyclic aliphatic amines also proved to be good substrates for the reaction, and were converted into the corresponding products in high yields (entries 3-6). However, higher temperature and a prolonged reaction time were required for the reactions with cyclic aromatic amines (entries 7 and 8). Furthermore, secondary acyclic aliphatic amines underwent the reaction smoothly in moderate yields (entries 9 and 10). The results suggested that the electronic and steric parameters of the substituents on the amines play a crucial role on the reaction.

Table 3 Substrate scope of amines[a]



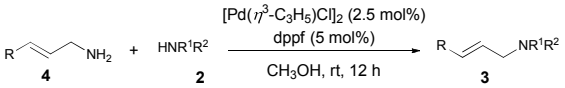
Entry	Amines	2	Product 3	Yield (%)[b]
1	NH_2Bn	**2b**	**3o**	63 + 6 bi-allyl amine
2		**2c**	**3p**	78 + trace bi-allyl amine
3		**2d**	**3q**	95
4		**2e**	**3r**	96
5		**2f**	**3s**	83
6		**2g**	**3t**	90
7[c]		**2h**	**3u**	83
8[c]		**2i**	**3v**	74
9	$NHBn_2$	**2j**	**3w**	65
10	$NH(n\text{-}Bu)_2$	**2k**	**3x**	52

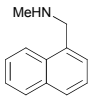
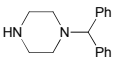
[a] **1a** (0.50 mmol, 1.0 equiv), amines (0.75 mmol, 1.5 equiv). [b] Isolated yields. [c] 50 °C instead of rt; 24 h.

To further expand the applicability of this methodology, we applied our catalytic system to the allylic amination with primary allylic amines (amine exchange). Success of the amine exchange depends on: (1) the C-N bond cleavage of allylic amines; (2) the thermodynamic equilibrium of the two allylic amines under our present catalytic system. To verify the feasibility of our proposed transformation, allylamines substituted with Ph, 4-MeC_6H_4, and 4-ClC_6H_4 were subjected to our reaction conditions, and the desired products were obtained in 81−96% yields (Table 4, entries 1-3). Subsequently, a range of primary and secondary amines were explored for amine exchange with prop-2-en-1-amine. And similar results were observed for amine exchange (entries 4-10).

A competition reaction with a 1:1 mixture of cinnamyl alcohol and cinnamyl amine was conducted, and the desired product was obtained in 97% yield with 86% cinnamyl alcohol recovery (please see SI). The result suggested that cinnamyl amine has higher reactivity than cinnamyl alcohol under the present reaction conditions.

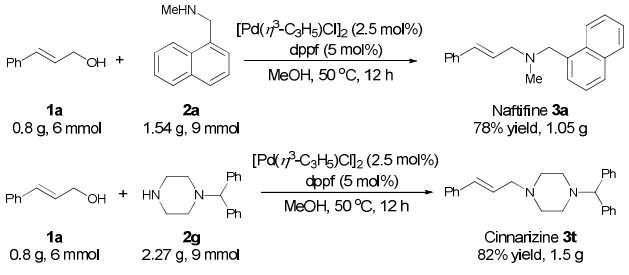
Table 4 Substrate scope of amines in amine exchange[a]



Entry	Amines	4	Product 3	Yield (%)[b]
1		**4a**: R = C_6H_5	**3a**	96
2		**4b**: R = 4-MeC_6H_4	**3y**	81
3		**4c**: R = 4-ClC_6H_4	**3z**	89
4		**4d**: R = H	**3aa**	78
5	NH_2Bn	**4d**: R = H	**3ab**	47 + 7 bi-allyl amine
6		**4d**: R = H	**3ac**	61
7		**4d**: R = H	**3ad**	82
8		**4d**: R = H	**3ae**	80
9		**4d**: R = H	**3af**	66
10	$NHBn_2$	**4d**: R = H	**3ag**	57

[a] Reaction of allylic amine (0.75 mmol, 1.5 equiv) with amines (0.50 mmol, 1.0 equiv) were performed using dppf (5.0 mol%) and [Pd(η^3-allyl)Cl]$_2$ (2.5 mol%) as a catalytic system in MeOH (2 mL) at rt for 12 h. [b] Isolated yields.

This methodology could be readily applied to a one-pot synthesis of two drugs, cinnarizine and naftifine, on a gram scale under mild reaction conditions (Scheme 2). Previous routes to these two agents involved several steps and/or higher reaction temperatures.[3] We reacted the commercially available cinnamyl alcohol and benzhydrylpiperazine/1-methyl-amino methyl naphthalene in the presence of [Pd(η^3-allyl)Cl]$_2$ (2.5 mol%) and dppf (5.0 mol%) in MeOH at 50 °C for 24 h. The antihistaminic drug, cinnarizine, and antifungal drug, naftifine, were obtained in 82% and 78% yield, respectively.



Scheme 2 Direct one-step synthesis of cinnarizine and naftifine.

To conclude, we have developed a hydrogen-bond-activated Pd-catalyzed allylic amination of allylic alcohols and allylic amines with primary and secondary amines under mild reaction conditions with good to excellent yields. The reaction proceeded in the absence of any activator and only water was produced as the sole by-product. This methodology can be

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applied to the efficient synthesis of the antihistaminic drug cinnarizine and the antifungal drug naftifine on a gram scale in one step.

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Direct Use of Allylic Alcohols and Allylic Amines in Palladium-Catalyzed Allylic Amination

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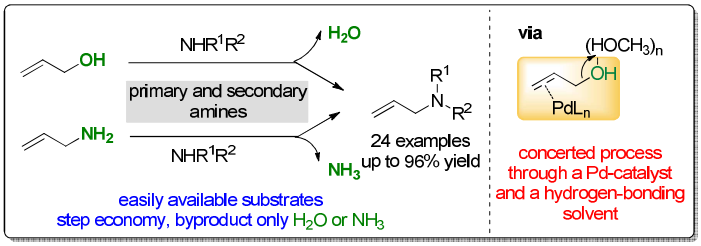

Allylic alcohols and allylic amines were directly utilized in a Pd-catalyzed hydrogen-bond-activated allylic amination under mild reaction conditions in the absence of any additives. The catalytic system is compatible with a variety of functional groups and can be used to prepare a wide range of linear allylic amines in good to excellent yields. Furthermore, this methodology can be easily applied to the one-step synthesis of two drugs, cinnarizine and naftifine, on a gram scale.