Homogeneous Catalysis

DOI: 10.1002/anie.201206319

Efficient and Convenient Palladium-Catalyzed Amination of Allylic Alcohols with N-Heterocycles**

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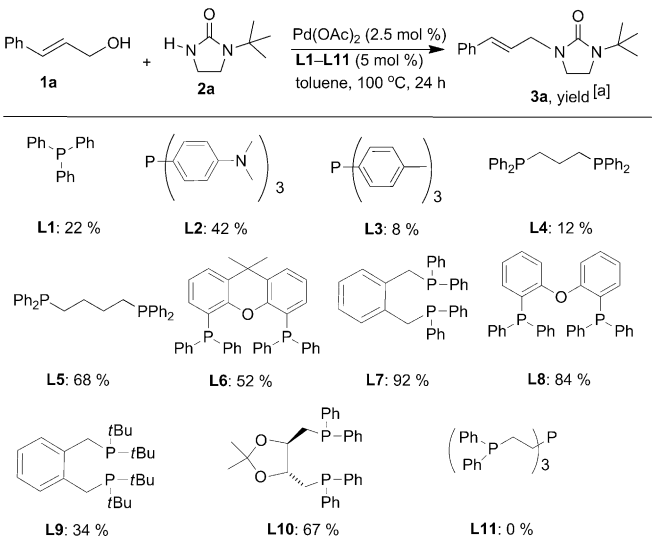
Based on the pioneering work by Tsuji and Trost,[1] palladium-catalyzed allylic substitution reactions have become a powerful tool for the construction of carbon–carbon and carbon–heteroatom (C–N, C–O, C–S) bonds in organic synthesis.[2] The utility of this method has been shown in the synthesis of numerous complex natural products and valuable intermediates for fine and speciality chemicals.[3] Elegant mechanistic investigations and the development of tailor-made homogeneous catalyst systems provide nowadays the basis for the control of regio- and enantioselectivity in various metal-catalyzed allylic substitution reactions. Apparently, no further methodological advancements are needed in this area. However with respect to more sustainable synthesis,[4] it is important to note that most such substitutions are performed with allyl acetates, carbonates, halides, sulfonates, phosphonates, etc. as substrates generating at least stoichiometric amounts of waste. Moreover, the corresponding activated substrates have to be prepared in additional steps lowering the overall efficiency of a given synthesis.[5] Alternatively, allylic alcohols might be used without preactivation of the hydroxy group, thus generating water as the only by-product. Hence, to streamline organic synthesis and to improve the atom efficiency, catalytic substitutions of nonactivated alcohols are gaining increasing interest.[6] In this respect, recent work by the research groups of Ozawa,[7a,b] Ikariya,[7c] Oshima,[7d] and others,[7e–i] is noteworthy.

Among the different types of allylic substitution reactions the synthesis of allylamines is of special interest.[8] In the last two decades the direct amination of alcohols has been intensively studied using Pd-,[3,7–8] Ru- and Ir-based catalysts applying the so-called "borrowing-hydrogen"[9] or "hydrogen autotransfer" principle.[10] Based on our previous work on the amination of alcohols,[11] we became interested in the catalytic amination of allylic alcohols, too. Thus, recently we developed a Pd/1,10-phenanthroline-based catalyst system that catalyzed the reaction of allylic alcohols and simple primary amines with high monoallylation selectivity.[12] Unfortunately, the amination of allylic alcohols with electron-deficient nitrogen nucleophiles did not work under these conditions owing to their poor nucleophilicity.[13] To our knowledge, to date, no palladium-catalyzed substitution reactions of allylic alcohols with amides or electron-deficient heterocycles are known. Although other transition metals or Lewis acids have been applied,[14] unfortunately most of these existing methods require large catalyst loadings, high reaction temperature or involve the use of additives for the amination reaction. Therefore, herein we present the first Pd-catalyst systems for the direct amination of allylic alcohols with a variety of N-heterocycles and related nitrogen nucleophiles, which does not need any additives and proceeds with high regioselectivity.

In our initial investigations we tested the amination of cinnamyl alcohol (**1a**, 1 mmol) with 1-*tert*-butylimidazolidin-2-one (**2a**, 1 mmol) in presence of $Pd(OAc)_2$ and different ligands **L1**–**L11** in toluene as solvent. When monodentate ligands (**L1**–**L3**) were used, this model reaction produced selectively 1-*tert*-butyl-3-cinnamylimidazolidin-2-one (**3a**) as the only regioisomer (8–42% yield) without any branched isomer of the corresponding amine (Scheme 1). The application of different bidentate ligands, such as 1,3-bis-(diphenylphosphino)propane (dppp, **L4**) was found to be not efficient, while the use of 1,4-bis(diphenylphosphino)butane (dppb, **L5**), Xantphos (**L6**), **L8**, 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (**L9**), and **L10** resulted in the isolation of the



Scheme 1. Screening of ligands for model reaction. [a] Yield of isolated product.

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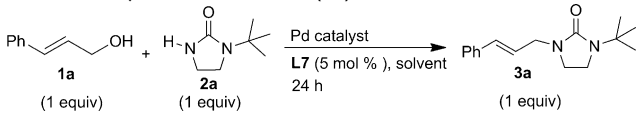
[**] The research has been funded by the State of Mecklenburg-Western Pomerania, the BMBF, and the DFG (Leibniz Prize). We thank Dr. W. Baumann, Dr. C. Fischer, S. Buchholz, S. Schareina, A. Koch, and S. Rossmeisl (all at LIKAT) for their excellent technical and analytical support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201206319.

desired product **3a** in improved yields from 34–84%. Notably, 1,2-bis(diphenylphosphinomethyl)benzene (**L7**) was identified as the most promising ligand and afforded **3a** in 92% yield.

Next, we evaluated the influence of different catalyst precursors, solvents, and temperatures for the model reaction using **L7** as ligand of choice (Table 1). Under similar reaction conditions, $Pd(OAc)_2$ gave best results among several other Pd precursors (Table 1, entries 1–4). Variation of solvents from toluene to *n*-heptane, 1,4-dioxane, and *tert*-amyl alcohol resulted in moderate to good yields of **3a** (Table 1, entries 5–7). It is possible to run the reaction at room temperature, albeit with significantly lower product yield (Table 1, entry 10).

Table 1: Palladium-catalyzed direct amination of cinnamyl alcohol (**1a**) with 1-*tert*-butylimidazolidin-2-one (**2a**) under various conditions.[a]

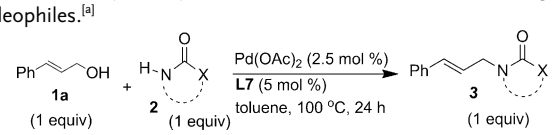


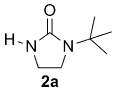
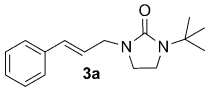
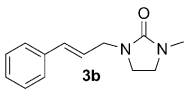
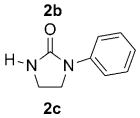
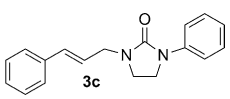
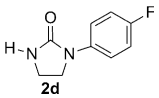
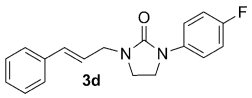
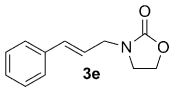
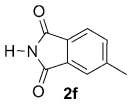
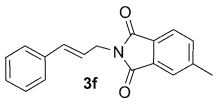
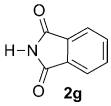
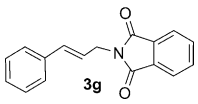
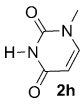
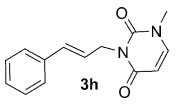
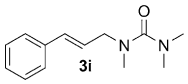
Entry	Catalyst (mol%)	Solvent	*T* [°C]	Yield [%][b]
1	$PdCl_2$ (2.5)	toluene	100	0
2	$[Pd(dba)_2]$ (2.5)	toluene	100	17
3	$Pd(OCOCF_3)_2$ (2.5)	toluene	100	30
4	$Pd(OAc)_2$ (2.5)	toluene	100	92
5	$Pd(OAc)_2$ (2.5)	*n*-heptane	100	67
6	$Pd(OAc)_2$ (2.5)	1,4-dioxane	100	50
7	$Pd(OAc)_2$ (2.5)	*t*-amyl alcohol	100	45
8	$Pd(OAc)_2$ (2.5)	toluene	80	55
9	$Pd(OAc)_2$ (2.5)	toluene	60	27
10	$Pd(OAc)_2$ (2.5)	toluene	25	12
11	$Pd(OAc)_2$ (1)	toluene	100	35
12[c]	$Pd(OAc)_2$ (2.5)	toluene	100	6
13	No catalyst	toluene	100	0

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), Pd catalyst (1–2.5 mol%), solvent (3.0 mL). [b] Yields of isolated products. [c] No ligand used. dba = (*E*,*E*)-dibenzylideneacetone.

After having promising results in hand for the model system, we applied the optimized protocol for the reaction of cinnamyl alcohol (**1a**) and a range of substituted N-heterocycles, such as imidazolidinones, oxazolidinone, imide, uracil, and urea derivatives. Selected results are summarized in Table 2 (entries 1–9). Reactions of methyl-, phenyl-, and 4-fluorophenyl-substituted imidazolidin-2-one (**2b**–**2d**) with cinnamyl alcohol (**1a**) preceded with similar efficiency and afforded **3b**–**3d** in yields of 69–78% (Table 2, entries 2–4). The electron-deficient oxazolidin-2-one **2e** was also found to be a good substrate and gave 75% yield of **3e** (Table 2, entry 5). Similarly, 4-methylphthalimide (**2f**) and phthalimide (**2g**) gave almost quantitative yields of **3f** and **3g** (Table 2, entries 6–7). Interestingly, the reaction of **1a** with biologically relevant 1-methyluracil (**2h**),[15] led to 3-cinnamyl-1-methyluracil (**3h**) in quantitative yield (Table 2, entry 8). Furthermore, substituted acyclic urea derivatives, such as *N*,*N*-trimethylurea (**2i**) also reacted under our optimized conditions and gave **3i** in 60% yield (Table 2, entry 9).

Table 2: Pd-catalyzed allylic substitution of **1a** with various nitrogen nucleophiles.[a]

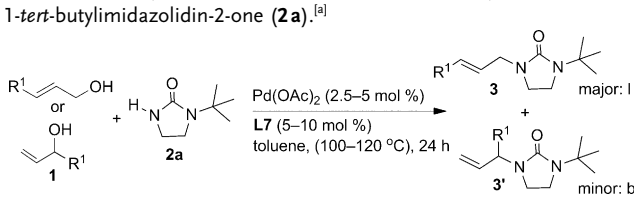


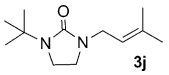
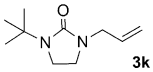
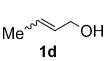
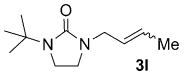
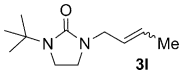
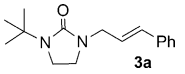
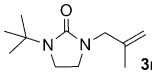
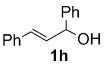
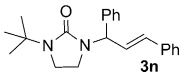
Entry	Nucleophiles **2**	Product **3**	Yield [%][b]
1			92
2			78
3			75
4			69
5			75
6			95
7			94
8			95
9			60

[a] General reaction conditions: **1a** (1 mmol), **2** (1 mmol), $Pd(OAc)_2$ (2.5 mol%), **L7** (5 mol%), toluene (3 mL), 100°C, 24 h. [b] Yields of isolated products.

Next, we turned our interest to the amination of more challenging aliphatic allylic alcohols, which are known to be less reactive. Here, we studied the regioselectivity of a variety of allylic alcohols bearing phenyl or methyl substituents at either α-, β-, or γ-positions. Reaction of γ,γ-dimethyl-substituted allylic alcohol (**1b**) with 1-*tert*-butylimidazolidin-2-one (**2a**) did not produce any promising yields of **3j** under the previously optimized conditions (Table 2). However, when the catalyst loading was increased to 5 mol% $Pd(OAc)_2$ and 10 mol% **L7** the product **3j** was isolated in 65% yield

Table 3: Pd-catalyzed direct substitution of different allylic alcohols with 1-*tert*-butylimidazolidin-2-one (**2a**).[a]



Entry	Allylic alcohol **1**	Product **3**	Yield [%][b]	l/b[h]
1[c]	 **1b**	 **3j**	65	98:2
2[d]	 **1c**	 **3k**	63	95:5
3[d,f]	 **1d**	 **3l**	65[g]	4:1
4[d]	 **1e**	 **3l**	65[g]	4:1
5[e]	 **1f**	 **3a**	80	>99:1
6[d]	 **1g**	 **3m**	70	–
7	 **1h**	 **3n**	42	–

[a] General reaction conditions: **1** (1–2 mmol), **2a** (1 mmol), $Pd(OAc)_2$ (5 mol%), **L7** (10 mol%), toluene (3 mL), 120°C, 24 h. [b] Yields of isolated products. [c] 1.5 equiv alcohol was used. [d] 2.0 equiv alcohol was used. [e] $Pd(OAc)_2$ (2.5 mol%), **L7** (5 mol%), 100°C were used. [f] *E*/*Z* mixture of **1d** (*E*/*Z* = 97:3) was used. [g] **3l** was obtained as an *E*/*Z* mixture (10:1). [h] Determined by GC–MS analysis.

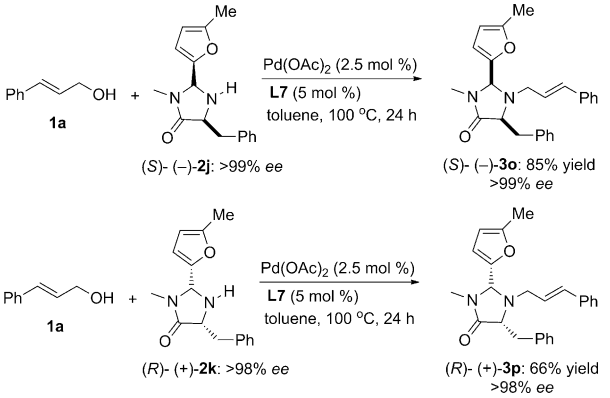
(Table 3, entry 1). Under analogous conditions the reaction of allylic alcohol (**1c**), γ-methyl-substituted allylic alcohol (**1d**), and α-methyl-substituted allylic alcohol (**1e**) afforded **3k** and **3l** in 63–65% yield (Table 3, entries 2–4). With regard to the mechanism it is important to note that the latter two reactions resulted both in the formation of the linear regioisomer **3l** as the major product (Table 3, entries 3–4).

In agreement with this observation, also the reaction of α-phenyl-substituted cinnamyl alcohol (**1f**) showed exclusive formation of the linear regioisomer **3a** (Table 3, entry 5) similar to the reaction of cinnamyl alcohol (**1a**) with **2a** (Table 2, entry 1).

Hence, we propose that the reactions take place via the same π-allylpalladium intermediate, and the regioselectivity is determined by the attack of the nucleophile on this common intermediate.

The reaction of β-methyl-substituted allylic alcohol with 1-*tert*-butylimidazolidin-2-one (**2a**) can only afford one regioisomer and gave 70% yield of **3m** (Table 3, entry 6). Furthermore, the sterically more hindered α,γ-diphenyl-substituted allylic alcohol (**1h**) gave in moderate yield the allylated products **3n** (Table 3, entry 7). As shown in Table 3, in some of these reactions we also observed the formation of a minor amount of the branched isomer in GC–MS analysis. In all reactions with lower yields of **3**, nonreacted allylic alcohol and 1-*tert*-butylimidazolidin-2-one were also recovered from the reaction mixture. In few cases we observed about 5–10% decomposition products from the respective alcohols.

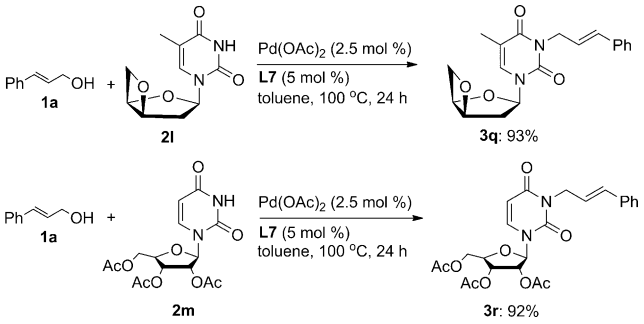
The general reactivity of different aromatic and aliphatic allylic alcohols with a variety of electron-poor N-heterocycles prompted us to check the utility of our protocol with chiral imidazolidinone derivatives. Indeed, the reaction of cinnamyl alcohol **1a**, with (*S*)-(−)-**2j** and (*R*)-(+)-**2k** resulted in the isolation of enantiomerically pure *N*-allylated imidazolidin-4-one (*S*)-(−)-**3o** and (*R*)-(+)-**3p** in excellent yields (Scheme 2).



Scheme 2. Pd-catalyzed N-allylation of chiral imidazolidinones.

Finally, we demonstrated the utility of this benign allylation protocol in the reaction of uridine and thymidine derivatives. These compounds belong to the most important class of biologically active N-heterocycles, found in nucleosides and nucleotides, which are key components of DNA and RNA. It is well-known that several uridine-containing N-heterocyclic natural products possess antitumor, antiviral, and antifungal properties.[16,17] Selected examples of such compounds are the thymidine analogue AZT, which is used for the treatment of AIDS;[16a] Eniluracil,[16b] which is widely used as anticancer drug; Capuramycin;[16c] FR-900493;[16d] and Caprazol.[16d] Moreover, uridine and its analogues are used for the synthesis of complex nucleoside antibiotics for drug development.[17a–d] To our delight, the reaction of cinnamyl alcohol (**1a**) with the thymidine derivative **2l** proceeded smoothly and gave 93% yield of *N*-allylated thymidine derivative **3q**, without affecting the sugar moiety (Scheme 3). Similarly, the reaction of the acetyl-protected uridine derivative **2m** afforded 92% yield of the *N*-allylated uridine **3r** (Scheme 3).

In summary, we have developed an efficient and convenient Pd-catalyzed amination of electron-poor N-heterocycles with allylic alcohols bearing aryl or alkyl substituents at either α-, β-, or γ-positions. The commercially available catalyst system consisting of $Pd(OAc)_2$/1,2-bis(diphenylphosphinomethyl)benzene allows for the straightforward formation of linear allylic amine derivatives with high regioselectivity. The reaction is atom-economic; environmentally benign, as water is the only by-product; and does not need any additives. As an



Scheme 3. Pd-catalyzed nucleophilic substitutions of thymidine and uridine derivatives.

example for the synthetic utility, the N-allylation of biologically important uridine and thymidine derivatives is shown.

Experimental Section

In an Ar atmosphere, an oven-dried Schlenk tube was charged with cinnamyl alcohol (**1a**, 1 mmol) and 1-*tert*-butylimidazolidin-2-one (**2a**, 1 mmol) and subsequently $Pd(OAc)_2$ (2.5 mol%) and **L7** (5 mol%) were added. Toluene (3 mL) and a magnetic stirrer bar were added and the reaction mixture was stirred at 100°C for 24 h. Then, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using ethyl acetate/hexane as eluent to afford **3a** (92%) as a colorless oil.

Received: August 7, 2012
Published online: September 28, 2012

Keywords: allylic substitution · amination · nitrogen heterocycles · palladium · sustainable chemistry

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