Asymmetric Allylic Amination

DOI: 10.1002/anie.201405511

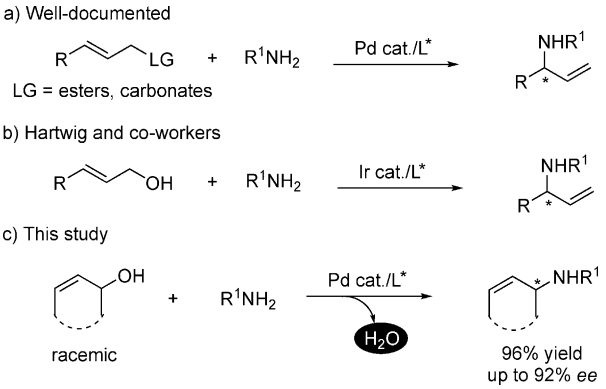
Cooperative Catalysis by Palladium and a Chiral Phosphoric Acid: Enantioselective Amination of Racemic Allylic Alcohols**

*Debasis Banerjee, Kathrin Junge, and Matthias Beller**

Abstract: *Cooperative catalysis by [Pd(dba)$_2$] and the chiral phosphoric acid* ***BA1*** *in combination with the phosphoramidite ligand* ***L8*** *enabled the efficient enantioselective amination of racemic allylic alcohols with a variety of functionalized amines. This catalytic protocol is highly regio- and stereoselective (up to e.r. 96:4) and furnishes valuable chiral amines in almost quantitative yield.*

Palladium-catalyzed asymmetric allylic substitution has become a highly valuable tool in organic synthesis and catalysis.[1] Following the pioneering studies by the research groups of Tsuji and Trost, this methodology has been expanded significantly in the last three decades, and now all kinds of nucleophiles can be efficiently coupled with various allylic electrophiles.[2] Among the different types of allylic substitution reactions, the synthesis of allylic amines is of special importance owing to the prevalence of this structural motif in pharmaceuticals and biologically active natural products.[3] Notably, in last decade, several elegant methods for selective asymmetric allylic amination with palladium-, ruthenium-, and iridium-based catalysts have been reported, including mechanistic investigations.[4] However, despite significant progress, most asymmetric allylic amination reactions rely on the preactivation of allylic alcohols. In general, such reactions are performed with allylic acetates, halides, and carbonates and consequently generate stoichiometric amounts of salt waste. The use of non-activated allylic alcohols in the enantioselective synthesis of chiral amines would streamline synthetic sequences and constitute an efficient, straightforward, and environmentally benign approach with water as the only by-product.[5] Unfortunately, owing to the poor leaving ability of the hydroxy group, higher reaction temperatures as well as external activators are required to activate the C–O bond, which limits such reactions to the formation of achiral products.[6]

The direct use of allylic alcohols for enantioselective amination reactions constitutes a highly challenging task and is still underdeveloped. Hartwig and co-workers introduced an iridium-catalyzed asymmetric amination of linear allylic alcohols activated by niobium ethoxide ($Nb(OEt)_5$) and triphenylborane (BPh_3) to give branched allylic amines with high regio- and enantioselectivity (Scheme 1),[7] and more recently, Carreira and co-workers described the iridium-catalyzed enantioselective amination of allylic alcohols with sulfamic acid as an ammonia equivalent.[8] To the best of our knowledge, no enantioselective amination of racemic allylic alcohols to afford optically active tertiary amines has been developed with palladium catalysts. Herein, we report an enantioselective amination of racemic alcohols with various amines in the presence of a Pd catalyst in combination with a chiral phosphoramidite ligand and a chiral phosphoric acid.



Scheme 1. Transition-metal-catalyzed enantioselective amination of allylic esters and alcohols. dba = dibenzylideneacetone.

As a result of our long-standing interest in the amination of alcohols[9] and hydroamination of olefins,[10] we recently became interested in the asymmetric allylic amination of racemic allylic alcohols. In our initial investigations, we treated racemic 2-cyclohexen-1-ol (**1a**) with aniline (**2a**) in the presence of [Pd(dba)$_2$] (5 mol%) and chiral phosphoramidite ligands[11] **L1**–**L8** (Scheme 2). Unfortunately, the application of the naphthyl Trost ligand **L1** or the chiral phosphoramidite ligands **L2**–**L4** provided negligible conversion into **3a**. However, the use of ligand **L5** with a 2-naphthyl substituent in the amine moiety proved beneficial, and **3a** was obtained in 25% yield with e.r. 56:49. Variation of the binol backbone to give the spiro ligand **L6** enhanced the catalytic activity, and the product was obtained in 75% yield with e.r. 62:38. Furthermore, the use of ligand **L7**, a diastereoisomer of **L2**, enabled the formation of **3a** in 57% yield with e.r. 60:35. To our delight, use of the phosphoramidite ligand **L8** with a 2-methoxyphenyl substituent in the amine moiety

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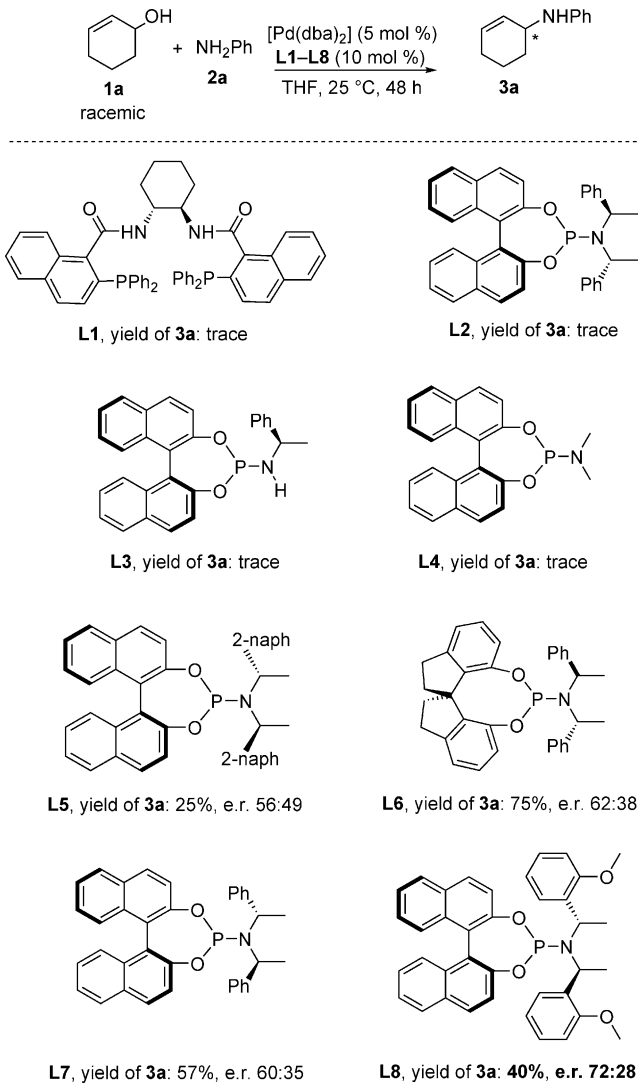
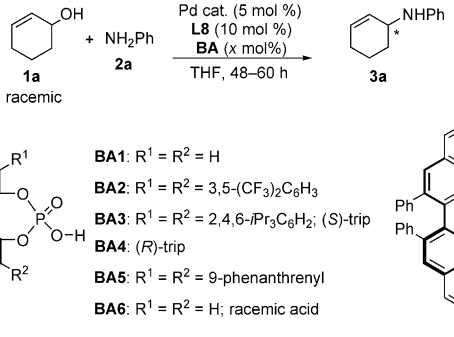
[**] This research has been funded by the State of Mecklenburg–Western Pomerania, the BMBF, and the DFG (Leibniz Prize). We thank Dr. W. Baumann, Dr. C. Fischer, S. Buchholz, S. Schareina, A. Koch, and S. Rossmeisl (all at LIKAT) for their excellent technical and analytical support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201405511.



Scheme 2. Investigation of ligands for the enantioselective allylic amination of 2-cyclohexen-1-ol.

Table 1: Development of an optimal catalyst system for the asymmetric amination of racemic 2-cyclohexen-1-ol.[a]



Entry	Pd catalyst	BA	Solvent	*T* [°C]	Yield [%][b]	e.r.[c]
1	$[Pd(dba)_2]$	**BA1**	THF	25	95	96:4
2	$[\{Pd(\pi\text{-cinnamyl})Cl\}_2]$	**BA1**	THF	25	0	n.d.
3	$[\{Pd(\pi\text{-allyl})Cl\}_2]$	**BA1**	THF	25	0	n.d.
4	$[Pd(PPh_3)_4]$	**BA1**	THF	25	40	–
5	$[Pd(dba)_2]$	**BA2**	THF	25	10	85:15
6	$[Pd(dba)_2]$	**BA3**	THF	25	25	78:22
7	$[Pd(dba)_2]$	**BA4**	THF	25	8	n.d.
8	$[Pd(dba)_2]$	**BA5**	THF	25	0	–
9	$[Pd(dba)_2]$	**BA6**	THF	25	20	80:20
10	$[Pd(dba)_2]$	**BA7**	THF	25	28	87:13
11	$[Pd(dba)_2]$	TFA	THF	25	10	79:21
12	$[Pd(dba)_2]$	**BA1**	CH_2Cl_2	25	0	–
13	$[Pd(dba)_2]$	**BA1**	1,4-dioxane	25	0	–
14	$[Pd(dba)_2]$	**BA1**	THF	10	90	95:5
15	–	**BA1**	THF	25	–	–
16[d]	$[Pd(dba)_2]$	**BA1**	THF	25	–	–

[a] Reaction conditions: **1a** (1 mmol), **2a** (0.25 mmol), Pd catalyst (5 mol%), **L8** (10 mol%), **BA** (5 mol%), solvent (1 mL), 10–25 °C. [b] Yield of the isolated product. [c] The enantiomeric ratio was determined by GC on a chiral stationary phase. n.d. = not determined. [d] The reaction was carried out without **L8**.

afforded **3a** in 40% yield with a more promising enantiomeric ratio (e.r. 72:28).

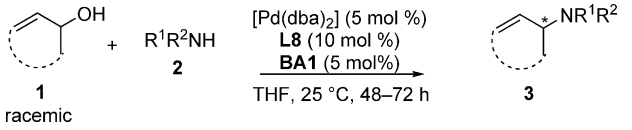
To improve the stereoselectivity of the transformation further, we studied the influence of different catalyst precursors, solvents, and additives on the model reaction. List and co-workers demonstrated that the stereoselectivity of asymmetric allylic alkylation reactions of aldehydes with allylic alcohols can be efficiently controlled by a suitable combination of a Pd complex and a chiral phosphoric acid.[12] It was proposed that the chiral phosphoric acid facilitates the formation of the active allyl palladium complex. Inspired by these studies, we tested the effect of a series of chiral phosphoric acids in combination with $[Pd(dba)_2]$ and ligand **L8** (Table 1). We were pleased to find that the use of 5 mol% of the chiral phosphoric acid **BA1** afforded **3a** in 95% yield with e.r. 96:4 (Table 1, entry 1)! Surprisingly, under similar reaction conditions with other palladium precursors, **3a** was formed in moderate yield with no selectivity or not at all (Table 1, entries 2–4).

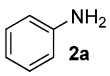
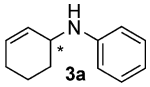
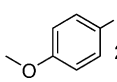
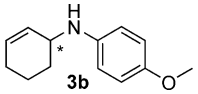
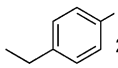
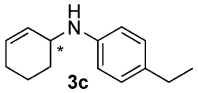
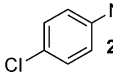
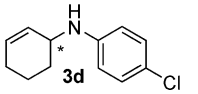
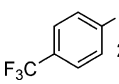
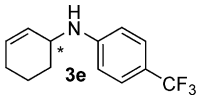
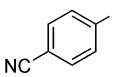
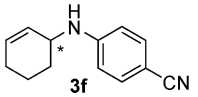
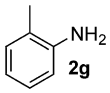
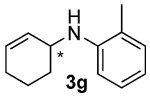
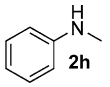
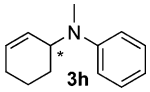
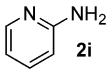
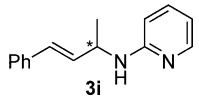
Next, we studied the influence of the steric and electronic effects of different chiral binaphthol-based phosphoric acid derivatives.[13] Application of the 3,3′-bis(trifluoromethylphenyl) derivative **BA2** and (*S*)-trip (**BA3**) under the optimal conditions resulted in the formation of **3a** in only 10 and 25% yield with e.r. 85:15 and 78:22, respectively (Table 1, entries 5 and 6). The ligand (*R*)-trip (**BA4**) offered even lower reactivity, thus suggesting the formation of a mismatched combination (Table 1, entry 7). Sterically hindered **BA5** and **BA7** also proved inactive towards enantioselective amination (Table 1, entries 8 and 10). Furthermore, the racemic phosphoric acid **BA6** as well as trifluoroacetic acid gave **3a** in only low yield with poor selectivity (Table 1, entries 9 and 11). The examination of different solvents (THF, dioxane, dichloromethane, and toluene) revealed that THF is a unique solvent for this enantioselective amination (Table 1, entries 12 and 13). Under optimal conditions, the amination reaction could also be carried out at lower temperature (10 °C); in this case **3a** was obtained in 90% yield with e.r. 95:5 (Table 1, entry 14). Control experiments with the individual components of the catalyst system suggested a strong synergistic

effect between the chiral phosphoric acid [Pd(dba)$_2$] (**BA1**) and the phosphoramidite ligand **L8** (Table 1, entries 1, 15, and 16).

Having established optimal reaction conditions, we explored the reaction of racemic 2-cyclohexen-1-ol (**1a**) with functionalized aniline derivatives substituted with electron-donating or electron-withdrawing substituents (Table 2). In the case of methoxy-, alkyl-, chloro-, trifluoromethyl-, and cyano-substituted aniline derivatives, products **3b–f** were formed in excellent yield (90–95%) with high enantioselectivity (e.r. 90:10–95:5; Table 2, entries 2–6). Notably, the reactions of **1a** with sterically hindered *o*-toluidine (**2g**) and secondary *N*-methylaniline (**2h**) afforded **3g**,**h** in almost quantitative yield with e.r. 94:6 and 91:9, respectively (Table 2, entries 7 and 8). The reaction of the heterocyclic amine 2-aminopyridine (**2i**) with 4-phenyl-2-butenol (**1b**) also proceeded in moderate yield and selectivity (Table 2, entry 9). In all reactions, no bisallylic amines were observed by GC–MS analysis of the crude reaction mixture. Whenever possible, we also recovered the unreacted starting materials. Unfortunately, under similar reaction conditions, we observed poor reactivity with aliphatic amines, probably owing to their higher nucleophilicity which leads to reduced activation of allylic alcohol.

Table 2: Palladium-catalyzed enantioselective amination of racemic allylic alcohols with amines.[a]

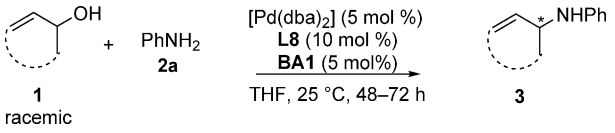


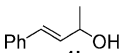
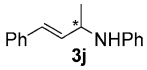
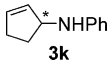
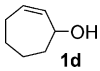
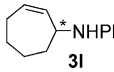
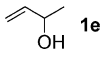
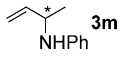
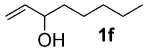
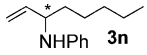
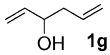
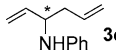
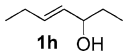
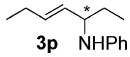
Entry	1	2	Product 3	Yield [%][b]	e.r.[c]
1	**1a**	 **2a**	 **3a**	95	96:4
2	**1a**	 **2b**	 **3b**	90	94:6
3	**1a**	 **2c**	 **3c**	92	95:5
4	**1a**	 **2d**	 **3d**	93	95:5
5	**1a**	 **2e**	 **3e**	95	92:8
6	**1a**	 **2f**	 **3f**	90	90:10
7	**1a**	 **2g**	 **3g**	96	94:6
8	**1a**	 **2h**	 **3h**	95	91:9
9[d]	**1b**	 **2i**	 **3i**	65	80:20

[a] Reaction conditions: **1** (1 mmol), **2** (0.25 mmol), Pd catalyst (5 mol%), **L8** (10 mol%), **BA1** (5 mol%), solvent (1 mL). [b] Yield of the isolated product. [c] The enantiomeric ratio was determined by HPLC or GC on a chiral stationary phase. [d] The reaction was performed at 40°C for 72 h.

To further demonstrate the generality of this novel protocol, we studied the scope of the reaction of acyclic and cyclic racemic alkyl allylic alcohols with aniline (Table 3). The reaction of 4-phenyl-2-butenol (**1b**) with **2a** led to **3j** in almost quantitative yield with e.r. 85:15 (Table 3, entry 1). Similarly, the reaction of 2-cyclopenten-1-ol (**1c**) and 2-cyclohepten-1-ol (**1d**) with aniline (**2a**) afforded **3k**,**l** in 94 and 60% yield with e.r. 92:8 and 87:13, respectively (Table 3, entries 2 and 3).

Table 3: Palladium-catalyzed enantioselective amination of racemic allylic alcohols.[a]



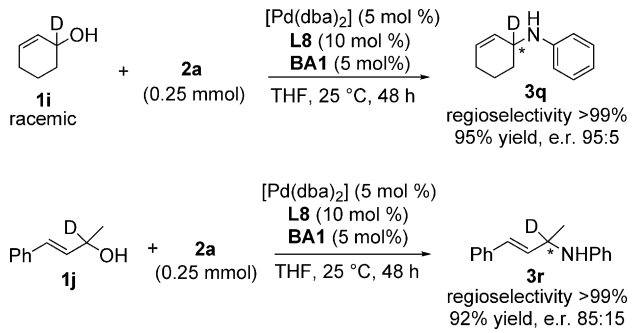
Entry	Alcohol 1	Product 3	Yield [%][b]	e.r.[c]
1[d]	 **1b**	 **3j**	95	85:15
2	 **1c**	 **3k**	94	92:8
3	 **1d**	 **3l**	60	87:13
4[e]	 **1e**	 **3m**	93	94:6
5[e]	 **1f**	 **3n**	95	96:4
6[e]	 **1g**	 **3o**	90	90:10
7[e]	 **1h**	 **3p**	76	94:6

[a] Reaction conditions: **1** (1 mmol), **2a** (0.25 mmol), Pd catalyst (5 mol%), **L8** (10 mol%), **BA1** (5 mol%), solvent (1 mL). [b] Yield of the isolated product. [c] The enantiomeric ratio was determined by HPLC or GC on a chiral stationary phase. [d] The reaction was performed at 40°C for 72 h. [e] The reaction was performed for 12 h.

We also explored the reactivity of more challenging secondary alkyl allylic alcohols. These substrates are commonly known to be less reactive and highly prone to form nonchiral linear products.[6] However, the reaction of 3-buten-2-ol (**1e**) with **2a** gave **3m** in 93% yield with e.r. 96:4 (Table 3, entry 4). Similar reactions of **2a** with 1-octen-3-ol (**1f**), 1,5-hexadien-3-ol (**1g**), and 2-hepten-4-ol (**1h**) also afforded the corresponding products **3n–p** in very good yields (76–95%) with e.r. 90:10–96:4 (Table 3, entries 5–7).[14] Notably, these reactions occurred with excellent (> 99%) regioselectivity for the branched isomer. However, in the case of **3p**, we observed

a minor amount (ca. 5%) of another isomer by GC–MS analysis of the crude reaction mixture (Table 3, entry 7).

We next treated the deuterated allylic alcohols **1i,j** with aniline under the optimized reaction conditions and were pleased to find that the reaction is indeed highly regio- and enantioselective (Scheme 3). Thus, exclusive formation of the



Scheme 3. Enantioselective amination of deuterated allylic alcohols.

chiral deuterated amines **3q,r** in almost quantitative yield with e.r. 95:5 and 85:15 was observed. It is proposed that the allylic palladium intermediate formed in situ is stabilized by the ligand, and that the rate of isomerization of the two allylic palladium intermediates is slower than the rate of nucleophilic attack, which resulted in the regioselective formation of allylic amines. Notably, we did not observe other regioisomers by GC–MS analysis of the crude reaction mixture. When the amination reaction was performed with optically active (*S*)-1-octen-3-ol, the corresponding allylic amine was formed in 92% yield with e.r. 96:4 (see Scheme S1 in the Supporting Information).

To gain further insight into the reaction mechanism, we prepared the defined complex [{Pd(π-cyclohexyl)Cl)}$_2$] and tested its behavior in the enantioselective amination in the presence of aniline, **L8**, and **BA1** (see Scheme S2). The reaction gave **3a** in 50% yield with e.r. 85:15. Note that when the amination reaction was performed with allylpalladium chloride dimer or palladium(π-cinnamyl) chloride dimer, we did not observe any desired reactivity (Table 1, entries 2 and 3). We believe that in the presence of chloride, stable palladium–allyl complexes form and do not undergo further amination, whereas in the presence of dibenzylideneacetone, the formation of a more active palladium–phosphate complex occurs.[15] Indeed, when the amination was performed with the defined palladium–phosphate complex **5**, the desired product was formed in 53% yield with e.r. 90:10 in the presence of aniline and the chiral phosphoramidite ligand **L8** (see Scheme S2).

In conclusion, we have developed an efficient enantioselective amination of racemic allylic alcohols with different functionalized anilines. Key to high enantioselectivity is cooperative catalysis by [Pd(dba)$_2$], a chiral phosphoric acid, and the specific phosphoramidite ligand **L8**. The reaction proceeded even with less reactive alkyl allylic alcohols and furnished a number of products in almost quantitative yield with excellent enantioselectivity.

Experimental Section

Under an argon atmosphere, 2-cyclohexen-1-ol (1 mmol) and aniline (0.25 mmol) were placed in an oven-dried Schlenk tube (10 mL), and freshly prepared [Pd(dba)$_2$] (5 mol%) and the phosphoric acid **BA1** (5 mol%) were added, followed by **L8** (10 mol%). Freshly distilled THF (1 mL) and a magnetic stirrer bar were then added, and the reaction mixture was stirred at 25°C for the reported time. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by silica-gel column chromatography with ethyl acetate/hexane as the eluent to afford the corresponding allylic amine derivatives.

Received: May 22, 2014
Revised: September 10, 2014
Published online: October 10, 2014

Keywords: allylic alcohols · asymmetric amination · chiral phosphoric acids · palladium · phosphoramidite ligands

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