Palladium-Catalyzed Three-Component Synthesis of Functionalized Allylamines by Intermolecular Tandem Carbopalladation–Amination

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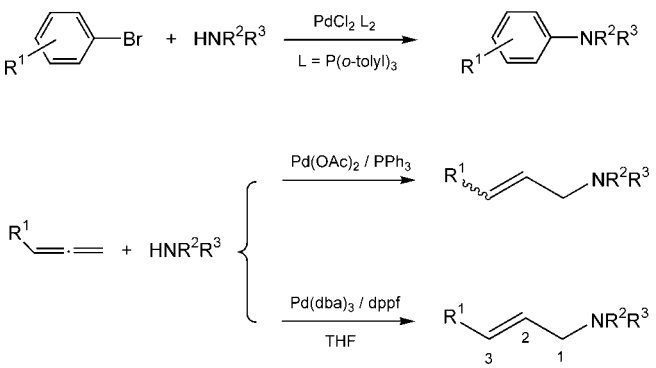
Abstract: Highly regio- and stereoselective formation of allylamines has been achieved through a three-component reaction between iodobenzene, an allene, and an amine in acetonitrile, catalyzed by *in situ* formed and by isolated palladium-diphosphine catalysts.

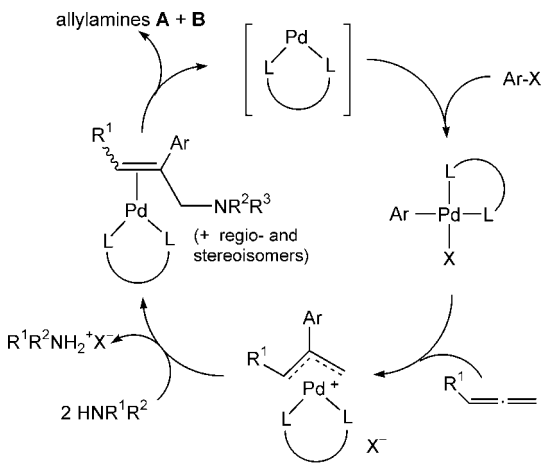
Keywords: allylamines; allylic amination; carbopalladation; homogeneous catalysis; palladium; P ligands

Catalytic carbon-nitrogen coupling is a highly desired chemical reaction and the development of suitable synthetic protocols for such reactions is currently receiving ample attention. Examples are the catalytic amination of aryl halides (Scheme 1)[1] and the amination of allylic substrates.[2]



Scheme 1. Selected transition metal-catalyzed C–N coupling reactions.

Allylamines are important synthetic targets which are found in many natural products; they often find application in products after subsequent transformations, e. g., amino acids, alkaloids.[3] Several stoichiometric and catalytic methods for the synthesis of a wide range of allylamines are known.[3,4,5] In these cases two components are employed and, usually, substituents are introduced at the allylic termini (positions 1 and 3). These can be chosen relatively freely, but few methods allow introduction of substituents at position 2 (see Scheme 1 for numbering). In one instance, a zirconocene-imine complex was reacted with an alkyne to provide stereochemically pure products. This procedure allows the choice of substituents at all three positions of the allylic moiety, but a severe drawback is the stoichiometric use of the zirconium compound involved.[5] Direct hydroamination of dienes and allenes would be a very attractive route to allylamines, but the selectivity is often very difficult to control and dimers or telomers are often obtained.[6]



Scheme 2. Anticipated reactions for a three-component intermolecular carbopalladation-amination of allenes to give allylamines.

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Insertion of allenes into palladium-carbon bonds of aryl-Pd and acyl-Pd compounds proceeds readily and protocols based on this reaction involving intramolecular attack by *N*-nucleophiles on the incipient π-allylpalladium complex to give valuable heterocyclic compounds are known.[7] An elegant example is the trapping of an allylpalladium(II) complex by internal *N*-nucleophiles in reactions of ω-2,3-dienyllactams with iodobenzene to give tetrahydropyrrolizin-3-ones and tetrahydro-2*H*-indolizin-3-ones.[7b] Intermolecular variants involving two components have also been established;[8] these proceed by intramolecular ring closure as the final step.

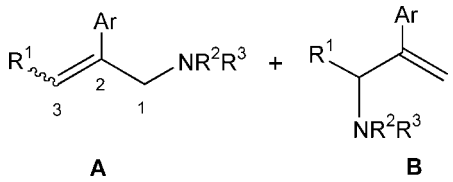
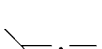
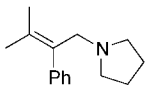
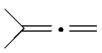
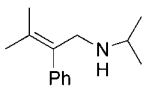
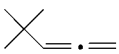
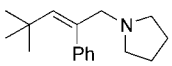
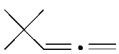
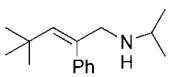
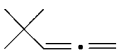
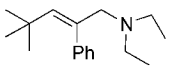
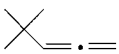
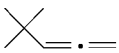
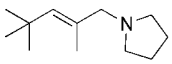
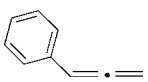
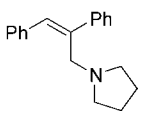
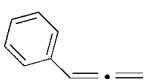
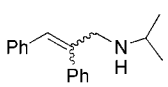


Figure 1.

We reasoned that, if the direct nucleophilic attack of the amine on the organic halide is slow (which is known to be the case for aryl halides) as compared to the allene insertion, one could envisage a *three*-component tandem-type reaction as indicated in

Table 1. Palladium-catalyzed three component synthesis of allylamines from 1,2-diene, iodobenzene and amine.

Entry	1,2-Diene	Amine	Product[a]	No	*E*/*Z*	Yield (%)[b]
1		pyrrolidine		**1**	n.a.	83
2		isopropylamine		**2**	n.a.	74[c]
3		pyrrolidine		**3**	100/0	95
4		isopropylamine		**4**	80/20	95
5		diethylamine		**5**	100/0	90[d]
6		diisopropylamine	No reaction	-	-	0
7[e]		pyrrolidine		**6**	70/30	9
8		pyrrolidine		**7**	34/66	93
9		isopropylamine		**8**	50/50	95

[a] Major isomer drawn.

[b] GC yields at 100% conversion; remainder is the allylic amine due to direct hydroamination (i.e., no oxidative addition of PhI).

[c] Remainder 20% hydroamination (R^1-CH=CH_2-NR^2R^3) and 6% β-elimination [H_2C=CH(Ph)-C(Me)=CH_2].

[d] Conversion 95%; remainder 5% PhI and 5% hydroamination.

[e] MeI was used as the electrophile, number refers to isolated yield.

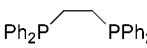
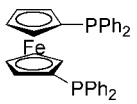
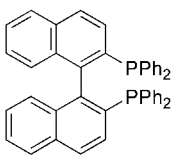
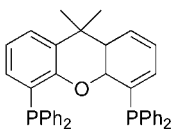
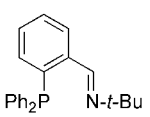
Scheme 2, leading to allylamines **A** and **B** (see Figure 1).[9] Shimizu and Tsuji have reported such a three-component reaction,[10] but it is limited to the use of non-volatile allenes and only the very nucleophilic pyrrolidine has been employed as the amine. When low-boiling allenes or diethylamine were used, this method led to a disappointing (<10%) yield. Hence, we chose to use a closed vessel (Ace tube) to carry out the allylic aminations, which resulted in good yields for a broader range of substrates. Furthermore, the catalyst precursor was varied (see below).

Indeed, reaction of iodobenzene with 3-methylbuta-1,2-diene and pyrrolidine or isopropylamine in acetonitrile in the presence of a palladium-diphosphine catalyst, obtained *in situ* from palladium acetate and 1,2-bis(dihenylphosphino)ethane (dppe), at 100 °C in an Ace pressure tube for 3 hours cleanly provided the respective allylamines **1** and **2** (Table 1, compare [10]) in good yield.

Regiospecificity was obtained in both the arylation at C2 and for the amination at C1, i. e., the expected nucleophilic substitution by the amine at the unsubstituted terminal allene carbon atom. Next, substrates with one substituent at the allenic terminus were selected to assess the regioselectivity for a more demanding substrate and in order to probe the stereoselectivity of the reaction. Thus, as shown in entries 3–5 of Table 1, reacting 4,4-dimethylpenta-1,2-diene according to the same protocol with iodobenzene and amines as in entries 1 and 2, led to good yields of the corresponding regiopure allylamines **3–5** with high stereoselectivity for the (*E*)-isomer. No reaction was observed with diisopropylamine or potassium diisopropylamide. However, diethylamine was a suitable nucleophile and gave (*E*)-**5** regio- and stereospecificly. Stereospecificity depends on the nucleophile; secondary, more basic amines give only the (*E*)-isomer, whereas isopropylamine gives an 80:20 *E/Z* mixture. This may be due to lower nucleophilicity and less steric hindrance (as compared to pyrrolidine and diethylamine), hence less stereodifferentiation in the nucleophilic attack on the intermediate *syn*- and *anti*-(π-allyl)palladium compounds.

Phenylpropadiene as the substrate gave similar results regarding the regiochemistry but generally much lower and opposite stereocontrol was obtained, with a slight preference for the *Z*-isomer. This may be explained by invoking the position of equilibrium between *syn*- and *anti*-isomers of the intermediate π-allyl-palladium complex (as compared to the situation for the products arising from 4,4-dimethylpenta-1,2-diene) and the relative rate of attack of the *N*-nucleo-

Table 2. Formation of allylamines as a function of the bidentate ligand in the catalyst.

Entry	Ligand	**7** (%)[a]	*E/Z*	**9** (%)[a]	t.o.f.[b]
1		93	34/66	0	2
2		97	18/82	2	20
3		97	19/81	2	31
4		97	16/84	2	35
5		95	41/59	5	19

[a] Substrate PhCH=C=CH_2. GC yields at 100% conversion; branched product, Ph-C(Me)=C(Ph)-N(C_4H_8)$_2$ (**9**), remainder is the allylic amine, Ph-CH=CH-CH_2-N(C_4H_8)$_2$ (**10**) due to direct hydroamination.

[b] Turnover frequency (mol product × mol catalyst^{-1} × h^{-1}).

phile on these species. Further studies must shed light on this conjecture.

Varying the organic halide to alkyl halides led to disappointing results. Reaction of methyl iodide (entry 7) with 4,4-dimethylpenta-1,2-diene and pyrrolidine gave only very low yields of **6**, whereas other alkyl iodides like *n*-butyl iodide gave irreproducible results and very low or no yield of the desired product at all. In these and other attempted cases we only obtained the alkylated amine (presumably via quaternization of the amine) and the hydroamination product arising from direct addition of the amine to the allene.

The composition of the catalyst, notably the type of donor atoms and their spacing in the ligand on palladium turned out to be an important parameter for the rate and stereoselectivity of the reaction. Whereas bidentate phosphine ligands provide reactive catalysts for the reaction discussed, employing a monodentate ligand such as triphenylphosphine, or the bidentate *N*-ligand Ar-bian[11] did not yield a reactive catalyst at all. In agreement with earlier observations,[10] the use of diphosphines is superior to monophosphines in these reactions, bidentate phosphine ligands appeared to be the ligands of choice. The *in situ* prepared palladium compounds combine excellent regio- and stereoselectivity to allylamines, as has been shown above for bisdiphenylphosphinoethane (dppe). From Table 2 it is seen that a catalyst derived from a bidentate mixed *P,N*-ligand is more active (in terms of turnover frequency) but gives lower stereoselectivity and more of the branched allylamine (**9**). However, higher activity and stereoselectivity (compared to dppe) were obtained for the catalysts derived from the bidentate diphosphines dppf, (*rac*)-Binap and Xanthphos.[12] Although these give also small amounts of **9** as the byproduct (entries 2–4), no contamination with the direct hydroamination product (**10**) was observed. Finally, the application of isolated, well-defined catalyst precursors Pd(Ph)I(diphos) obtained from oxidative addition of iodobenzene to a zero-valent Pd-precursor in the presence of dppf or Binap gave similar or slightly better results in terms of selectivity and yield, but catalysis was faster. This aspect will be elucidated in a forthcoming paper.

In conclusion, a highly regio- and stereoselective three-component palladium-catalyzed synthesis of allylamines has been achieved. Bidentate phosphines are the preferred ligands, the composition and structure of which greatly influence the stereoselectivity and rate of the reaction. Mechanistic aspects and alternative bidentate ligands as well as the application of defined precatalystst are currently subject of our continuing investigations.

Experimental Section

General Procedure

To 10 mL of acetonitrile (distilled from CaH_2) in an Ace pressure tube (35 mL) was added, under stirring, 14 mg (62 μmol, 2.5 mol %) of $Pd(OAc)_2$, 37 mg (93 μmol) of dppe (or similar amounts for other ligands), 0.28 mL (0.51 g, 2.5 mmol) of iodobenzene, 2.75 mmol (1.1 equivalent) of the appropriate 1,2-diene and 1 mL of the appropriate amine (ca. 4–5 equivalents) under a nitrogen atmosphere. The pressure tube was closed and heated to 100 °C in an oil bath. Samples were taken at regular intervals, by cooling the tube to 20 °C before opening it. Samples were passed over a short silica column and the composition was determined by use of GC–MS. The composition of the reaction mixture was determined by the use of GC–MS, ^{1}H and ^{13}C NMR. The crude product could be purified by use of flash chromatography, using silica gel as column material and mixtures of hexanes/ether as eluent. Yields of the pure products were about 25% lower than the GC-yields indicated in Table 1.

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