Synthetic Methods

DOI: 10.1002/anie.200903178

Synthesis of Aziridines by Palladium-Catalyzed Reactions of Allylamines with Aryl and Alkenyl Halides: Evidence of a *syn*-Carboamination Pathway**

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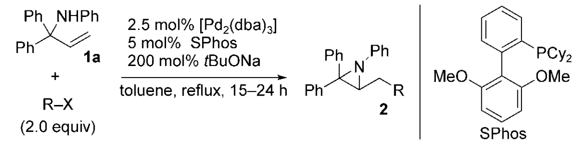
Palladium-catalyzed intramolecular carboetherification or carboamination reactions of alkenes with organic halides emerged as an attractive method to construct heterocycles, forming both carbon–heteroatom and carbon–carbon bonds in a single operation.[1] A number of five-membered heterocycles have been synthesized by this methodology,[2,3] however, the preparation of strained three-membered heterocycles has remained a challenge. We have previously reported palladium-catalyzed carboetherification reactions of tertiary allyl alcohols with aryl or alkenyl halides, which provide multisubstituted epoxides.[4] We expected that the reaction could be extended to carboamination for the synthesis of aziridines starting from allylamines. Herein we present our preliminary results of the carboamination along with evidence for a plausible reaction mechanism.

Our investigation began with a reaction of *N*-phenylallylamine **1a** bearing two phenyl groups at the allylic position (Table 1). Treatment of **1a** with bromobenzene in the presence of sodium *tert*-butoxide under palladium catalysis led to aziridination and C–C bond formation, providing the corresponding arylated aziridine **2a** in 98% yield (Table 1, entry 1). In contrast to our previous epoxidation reactions, the aziridination reaction did not suffer from a competitive Mizoroki–Heck reaction.[4] A wide range of aryl bromides and chlorides were incorporated into the corresponding aziridines **2a**–**2h** in excellent yields (Table 1, entries 2–9). Alkenyl chlorides also proved to be suitable substrates for the aziridination reactions (Table 1, entries 10 and 11).

The reactions of several *N*-arylallylamines with bromobenzene were then examined (Table 2). The electronic nature of aryl substituents on the nitrogen atom did not affect the efficiency of the reaction (Table 2, entries 1 and 2). Gratifyingly, alkyl-substituted allylamines **1d** and **1e** also underwent the reaction in satisfactory yields (Table 2, entries 3 and 4).

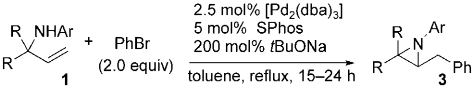
Table 1: Scope of the aryl and alkenyl halides in the palladium-catalyzed aziridination/arylation or aziridination/alkenylation with **1a**.



Entry	R–X	**2**	Yield [%][a]
1	C_6H_5Br	**2a**	98
2	C_6H_5Cl	**2a**	98
3	$1\text{-}C_{10}H_7Br$	**2b**	90
4	$2\text{-}MeOC_6H_4Br$	**2c**	83
5	$4\text{-}MeOC_6H_4Br$	**2d**	97
6	$4\text{-}Me_2NC_6H_4Br$	**2e**	88
7	$4\text{-}F_3CC_6H_4Cl$	**2f**	99
8	$4\text{-}(tBuO_2C)C_6H_4Cl$	**2g**	81
9	$4\text{-}(Et_2NOC)C_6H_4Cl$	**2h**	81
10	$(CH_3)_2C{=}CHCl$	**2i**	94
11	$(E)\text{-}n\text{-}C_5H_{11}CH{=}CHCl$	**2j**	90

[a] Yield of isolated product. Cy = cyclohexyl, dba = dibenzylideneacetone.

Table 2: Reactions with various *N*-arylallylamines with bromobenzene.



Entry	R	Ar	**1**	**3**	Yield [%][a]
1	Ph	$4\text{-}MeOC_6H_4$	**1b**	**3a**	92
2	Ph	$4\text{-}FC_6H_4$	**1c**	**3b**	96
3	$n\text{-}C_3H_7$	Ph	**1d**	**3c**	92
4	$\text{-}(CH_2)_5\text{-}$	Ph	**1e**	**3d**	76

[a] Yield of isolated product.

Next, we turned our attention to reactions of allylamines bearing a stereogenic center at the aminated carbon atom, in which two diastereomers could be obtained (Table 3). It was found that the larger substituent, R^L, and the benzyl moiety were oriented in a *cis* configuration in the major diastereomer.[5] Interestingly, the major diastereomer obtained in the aziridination reaction possessed a configuration opposite to that of the epoxides.[4] For instance, the reaction with **1f** afforded **4a** as a single diastereomer in 90% yield (Table 3, entry 1). Moreover, allylamine **1g** bearing a trifluoromethyl group also took part in the reaction with high diastereoselectivity (Table 3, entry 2). However, both yield and diastereo-

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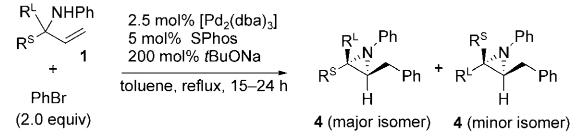
[**] This work was supported by Grants-in-Aid for Scientific Research from MEXT and JSPS. S.H. acknowledges JSPS for financial support. H.Y. acknowledges financial support from Eisai and Kyoto University.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200903178.

Table 3: Diastereoselective synthesis of aziridines.

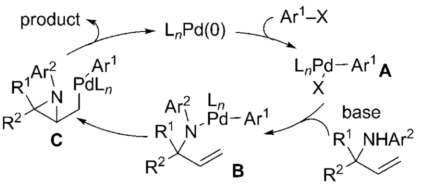


Entry	R^L	R^S	**1**	**4**	Yield [%][a]	d.r.
1	Ph	Me	**1f**	**4a**	90	>99:1
2	Ph	CF$_3$	**1g**	**4b**	90	93:7
3[b]	tBu	Me	**1h**	**4c**	42	59:41

[a] Yield of isolated product. [b] Xylene was used instead of toluene. An amount of 47% of **1h** was recovered .

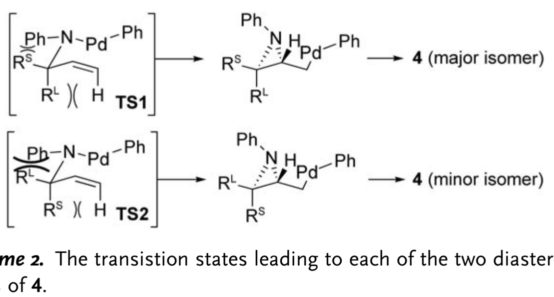
selectivity diminished when the more bulky *tert*-butyl-substituted allylamine **1h** was used as a substrate (Table 3, entry 3).

A mechanism of the reaction based on related precedent[1,2,4] is proposed as shown in Scheme 1. Initial oxidative addition of aryl halide to zerovalent palladium occurs to provide arylpalladium halide **A**. Subsequent ligand exchange between **A** and allylamine in the presence of sodium *tert*-butoxide affords palladium amide **B**. It seems likely that **B** would undergo reductive elimination to give the N-arylated product under the reaction conditions.[6] However, intramolecular coordination of the alkene moiety of **B** to the palladium center would prevent such a reductive elimination. The coordination and subsequent *syn* aminopalladation then furnishes alkylpalladium intermediate **C**.[7] Finally, reductive elimination from **C** takes place to give the corresponding aziridine and to regenerate Pd^0.



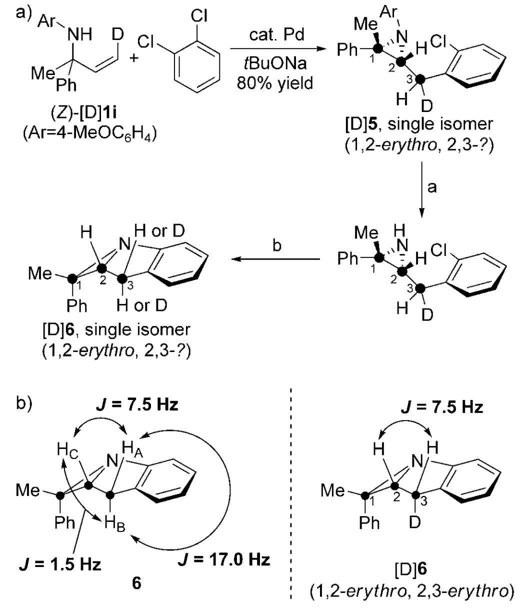
Scheme 1. Plausible reaction mechanism.

The observed diastereoselectivity in Table 3 could be explained as follows (Scheme 2). There are two presumable chair-like transition states, **TS1** and **TS2**, in the aminopalladation step, in which diastereoselectivity would be determined. Two sets of steric interactions should be considered in each of the two transition states: one is 1,3-allylic interaction between the pseudoaxial substituent, R^L or R^S, and the hydrogen atom at the alkene terminus, and the other is 1,2-pseudoequatorial repulsion between the phenyl group attached to the nitrogen atom and either R^L or R^S. Generally, **TS1** would be more favorable because of its smaller repulsion energy relative to that of **TS2**, which involves a larger repulsive interaction between R^L and the phenyl group (Table 3, entries 1 and 2). However, as R^L becomes much bulkier (Table 3, entry 3), the 1,3-allylic interaction cannot be negligible in **TS1**. As a result, the difference of the energy between the two transition states would be smaller, leading to the lower diastereoselectivity in the case of the reaction with **1h**.



Scheme 2. The transistion states leading to each of the two diastereomers of **4**.

As described above, we hypothesize that the reaction proceeds through *syn* aminopalladation of the palladium amide intermediate **B**. However, an intermolecular *anti*-aminopalladation pathway[8] is also conceivable. To confirm *syn* aminopalladation, we performed the reaction of (*Z*)-[D]**1i** with 1,2-dichlorobenzene (Scheme 3a). As a consequence, aziridine [D]**5** bearing three stereogenic centers was obtained as a single diastereomer. The relative configuration of **5** on the aziridine ring would be *erythro*, the same as **4a**.[9] The other relative configuration between the secondary aminated carbon atom and the deuterium-substituted carbon center (2,3-position) was not known at this stage and was determined after further derivatization. Oxidative removal of the 4-methoxyphenyl group and subsequent intramolecular amination of the aryl chloride gave an azabicyclo[3.1.0]hexane derivative [D]**6**. The corresponding nondeuterated analogue **6** was prepared in the same manner. The rigid conformation of **6** gave us characteristic coupling constants in the ^{1}H NMR spectrum, allowing assignment of the signals corresponding to H$_A$, H$_B$, and H$_C$ (Scheme 3b, left).[10] In contrast, the H$_B$ signal was not observed in the ^{1}H NMR spectrum of [D]**6** (Scheme 3b, right). Thus, the

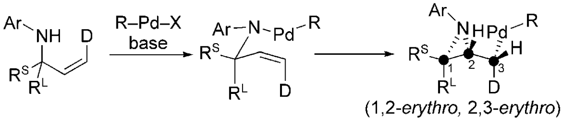


Scheme 3. Validation of the reaction mechanism. a) Ce(NH$_4$)$_2$(NO$_3$)$_6$, MeCN/H$_2$O, 0°C, 65%; b) cat. [Pd$_2$(dba)$_3$]/SPhos, K$_3$PO$_4$, toluene, reflux, 28%. b) ^{1}H NMR coupling constant analysis of both **6** and [D]**6**.

relative stereochemistry of the newly created stereogenic centers of [D]**6** was assigned as *erythro*. Therefore, [D]**5** should have a 1,2-*erythro,* 2,3-*erythro* configuration.

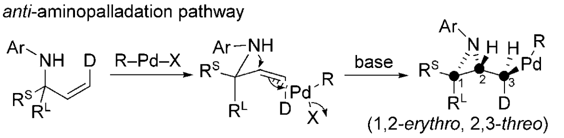
Suppose that the aminopalladation reaction proceeds in a *syn* fashion, (1,2-*erythro*, 2,3-*erythro*)-[D]**5** would be produced [Eq. (1)]. In contrast, the *anti*-aminopalladation pathway would result in the formation of (1,2-*erythro,* 2,3-*threo*)-[D]**5** [Eq. (2)]. Therefore, the experimental result is consistent with our hypothesis.

syn-aminopalladation pathway



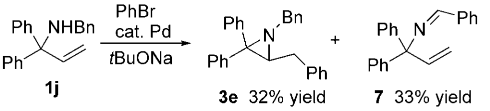
(1)

anti-aminopalladation pathway

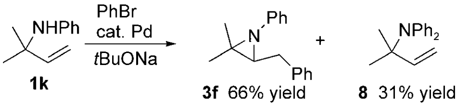


(2)

In addition, the reaction of **1j**, bearing a benzyl moiety on the nitrogen atom, provided a mixture of the aziridinated product **3e** and imine **7**, which would be generated from β-hydride elimination from the palladium amide intermediate corresponding to **B** in Scheme 1 [Eq. (3); Bn = benzyl]. Moreover, the reaction of **1k** gave aziridine **3f** along with the N-arylated allylamine **8** [Eq. (4)]. The results are also suggestive of the existence of the palladium amide intermediate.



(3)



(4)

In conclusion, we have found a new synthetic method for the preparation of aziridines by palladium-catalyzed reactions of allylamines with aryl or alkenyl halides. The reaction proceeds through *syn* aminopalladation, producing carbon–nitrogen bond with concomitant carbon–carbon bond formation. Synthesis of other strained hetero- and carbocycles by the methodology are currently under investigation in our laboratory.

Experimental Section

Typical procedure for palladium-catalyzed reactions of allylamines with aryl or alkenyl halides: The reaction of *N*-(1,1-diphenyl-2-propenyl)aniline (**1a**) with bromobenzene (Table 1, entry 1) is representative. Sodium *tert*-butoxide (0.058 g, 0.60 mmol) was added to a 30 mL two-necked reaction flask equipped with a Dimroth condenser and was dried by heating for 1 min. [Tris(dibenzylideneacetone)]dipalladium (6.9 mg, 0.0075 mmol) and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos, 6.2 mg, 0.015 mmol) were added to the flask, and the flask was filled with argon by using the standard Schlenck technique. Toluene (1.0 mL) was then added to the reaction mixture at room temperature. After the suspension was stirred for 10 min, **1a** (0.0856 g 0.30 mmol) and bromobenzene (0.0942 g, 0.60 mmol) were dissolved in toluene (2.0 mL) and then added to the flask at ambient temperature. The mixture was heated at reflux for 15 h with an oil bath. After the flask was cooled to room temperature, water (20 mL) was added to quench the reaction. The mixture was extracted with *n*-hexane/AcOEt = 5:1 three times. The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure. The resulting brown residue was purified by silica gel column chromatography under basic conditions (silica gel 60N was used with an eluent (*n*-hexane/AcOEt/triethylamine = 30:1:0.1)) to provide 3-benzyl-1,2,2-triphenylaziridine **2a** (0.106 g, 0.294 mmol, 98 %).

Received: June 12, 2009
Published online: August 28, 2009

Keywords: allylamines · aziridines · carboamination · palladium

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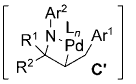
[5] The relative configuration of **4** was assigned by X-ray crystallographic analysis and NOE experiments. See the Supporting Information for details.

[6] Palladium amide intermediates bearing a bulky monophosphine ligand are known to undergo rapid reductive elimination to produce N-arylated products: a) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438–6461; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361; b) M. Yamashita, J. F. Hartwig, *J. Am. Chem. Soc.* **2004**, *126*, 5344–5345.

[7] We cannot exclude another possibility in which the reaction proceeds through *syn* carbopalladation, yielding azapalladacyclobutane **C′**. However, examples of reductive elimination to form an C_{sp^3}–N bond are rare. In contrast, *syn* aminopalladation and subsequent reductive elimination from **C** is a prevailing pathway as shown in reference [1].



[8] Although *anti* aminopalladation of olefin has been well studied, the reactions of amines tend to suffer from catalyst deactivation by the strong coordination of amine to the palladium center, except for the reaction of a substrate bearing a electron-withdrawing group on the nitrogen center. For leading reviews: a) L. S. Hegedus, *Tetrahedron* **1984**, *40*, 2415–2434; b) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675–704.

[9] For the unambiguous *erythro*/*threo* nomenclature, see: R. Noyori, I. Nishida, J. Sakata, *J. Am. Chem. Soc.* **1981**, *103*, 2106–2108.

[10] See the Supporting Information for more details.