Heterocycle Synthesis

Palladium-Catalyzed Synthesis of *N*-Aryl Pyrrolidines from γ-(*N*-Arylamino) Alkenes: Evidence for Chemoselective Alkene Insertion into Pd–N Bonds**

*Joshua E. Ney and John P. Wolfe**

In recent years, palladium(aryl)(amido) complexes have been shown to serve as key intermediates in the synthesis of aniline derivatives.[1] Although the propensity of these intermediates to undergo C–N bond-forming reductive elimination has been well established,[1] small molecule (alkene) insertion reactions of these complexes have been largely unexplored and have not been exploited in catalytic processes.[2] In fact, only a single example of the stoichiometric insertion of an activated alkyne into an isolated [Pd(Ar)(NR_2)] complex has been reported,[2b] and insertions of alkenes have not been demonstrated. Herein we describe a new, stereoselective, palladium-catalyzed synthesis of pyrrolidines from γ-(*N*-arylamino) alkenes and aryl bromides, and present mechanistic evidence that suggests the transformation proceeds by a chemoselective intramolecular insertion of an unactivated alkene into the Pd–N bond of an intermediate [Pd(Ar)(NRR′)] complex.[3] This reaction allows convergent access to substituted pyrrolidines, which are found in a variety of natural products.[4] In contrast to most methods available for the synthesis of substituted pyrrolidines,[5] this reaction effects intramolecular C–N bond formation with concomitant intermolecular formation of a C1′–C bond.[6]

In preliminary studies we employed γ-aminoalkene substrates with *N*-aryl substituents because of their ease of preparation and handling. After optimization of the reaction conditions we found that the reaction of *N*-phenyl-4-pentenylamine (**1a**) with 2-bromonaphthalene in the presence of NaO*t*Bu and a catalytic amount of [$Pd_2(dba)_3$]/dppb (1 mol%; dppb = 1,4-bis(diphenylphosphanyl)butane) at 60°C in toluene afforded the desired *N*-aryl 2-(β-naphthylmethyl)pyrrolidine **2a** and regioisomeric product **3a** in 94% yield and a 25:1 ratio [Eq. (1)].

As shown in Table 1, the reactions of electron-rich, electron-neutral, and electron-deficient *N*-aryl amine derivatives with a variety of aryl bromide coupling partners proceeded in good yield. A number of functional groups are

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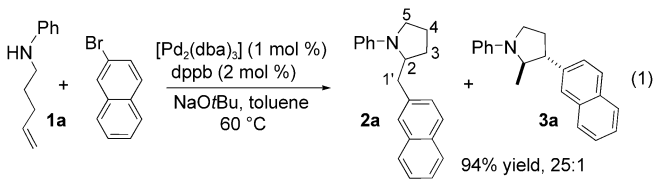
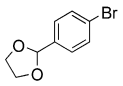
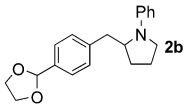
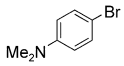
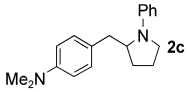
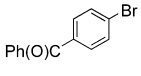
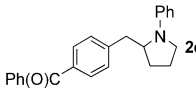
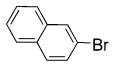
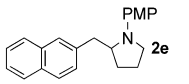
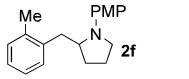
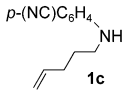
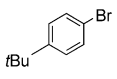
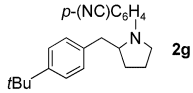
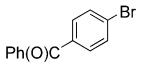
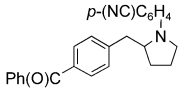
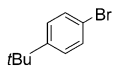
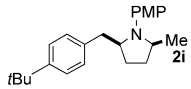
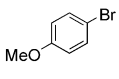
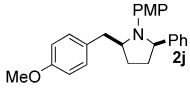
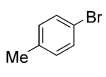
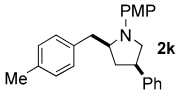
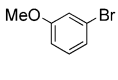
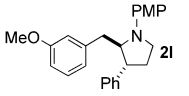


Table 1: Palladium-catalyzed synthesis of pyrrolidines.[a]

Entry	Amine	Aryl bromide	Product	2/3	Yield [%]
1				16:1	73
2	**1a**			17:1	81[b]
3	**1a**			100:1	45
4				14:1	67
5	**1b**			35:1	75
6				100:1	78
7	**1c**			>100:1	86
8				10:1	66[c] (d.r. >20:1)
9				10:1	72[c] (d.r. >20:1)
10				8:1	88[c] (d.r. 2:1)
11				10:1	68[c,d] (d.r. >20:1)

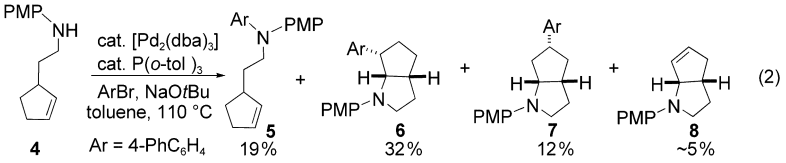
[a] Conditions: amine (1.0 equiv), ArBr (1.1–1.3 equiv), NaO*t*Bu (1.1–1.3 equiv), $[Pd_2(dba)_3]$ (1 mol%), dppb (2 mol%), toluene (0.25 M), 60 °C. [b] This material contained a second, unidentified regioisomer in approximately 3% yield. [c] Reaction conducted at 100 °C; dppe used in place of dppb. [d] This material contained *N*-(PMP)-2-(3-methoxybenzyl)-3-phenylpyrrole in approximately 8% yield. dppe = 1,4-bis(diphenylphosphanyl)ethane, PMP = 4-methoxyphenyl.

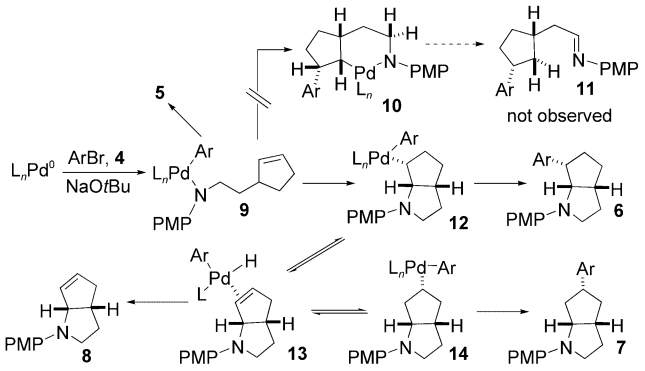
tolerated, including nitriles, nonenolizable ketones, and acetals. The main side products in these reactions are arenes that result from reduction of the aryl bromide[7] and *N*,*N*-diaryl amines that presumably form through Pd-catalyzed N-arylation of the substrate.[1] Side products resulting from Heck arylation of the alkene are generally not observed. These results contrast with those of previously described Pd-catalyzed reactions of γ-(*N*-benzylamino)alkenes with aryl iodides, which have been reported to afford exclusively products resulting from Heck arylation of the alkene.[8]

In most cases examined the cyclizations proceed with good levels of diastereoselectivity. The 3-substituted alkenyl amine **1g** underwent cyclization with >20:1 diastereoselectivity to provide the *trans*-2,3-disubstituted product **2l** (Table 1, entry 11),[9] and reactions of the 1-substituted alkenyl amines **1d** and **1e** gave the *cis*-2,5-disubstituted pyrrolidines **2i** and **2j** with d.r. >20:1 (Table 1, entries 8–9). In contrast, the C2-substituted amine **1f** reacted with only modest (2:1) *cis* stereoselectivity for the 2,4-disubstituted product **2k** (Table 1, entry 10).

The ratio of the regioisomeric products **2**/**3** of the cyclization reactions typically ranged from 10:1 to 25:1 for substrates with terminal alkenes, although in some instances selectivities of up to >100:1 were observed.[10] However, reactions of substrates with internal alkenes provided complex mixtures of regioisomeric products. Interestingly, the reaction of **4** with 4-bromobiphenyl in the presence of catalytic $[Pd_2(dba)_3]$/P(*o*-tol)$_3$ afforded a mixture of four products [Eq. (2)].[11] The desired 6-aryl pyrrolizidine product **6** was formed as the major regioisomer. A substantial amount of the 5-aryl regioisomer **7** was also isolated, along with a small amount of the unsaturated pyrrolizidine **8**. The use of dppb or dppe as a ligand led to the formation of increased amounts of **8** relative to the other products.[11,12]

Although the yield of the desired regioisomer **6** is modest, these results provide important information about the mechanism of the cyclization reaction. This transformation presumably occurs through initial oxidative addition of the aryl bromide to Pd^0 followed by reaction of the resulting complex with the substrate and base to afford **9** (Scheme 1).[1] A *syn* insertion of the alkene into the Pd–C bond of **9** would provide **10**. However, products **7** and **8** can not derive from **10**; C–C bond-forming alkene-insertion reactions are generally





Scheme 1. Proposed mechanism.

not reversible.[13] Furthermore, if the alkene underwent insertion into the metal–carbon bond to give **10**, the use of ligands that decrease the rate of reductive elimination, such as dppe,[12] would not provide increased amounts of **8** as is observed. A *syn* β-hydride elimination[13] of the intermediate **10** would instead afford the arylated imine **11**, which is not detected.[11]

A more reasonable pathway, which would account for all products formed in the reaction, involves *syn* insertion of the alkene into the Pd–N bond in **9** to afford **12** (Scheme 1).[2] Complex **12** could either undergo C–C bond-forming reductive elimination with retention of configuration to afford the desired product **6**,[14] or could undergo reversible β-hydride elimination to give the alkene complex **13**.[13] Reinsertion of the alkene into the Pd–H bond with reversal of regiochemistry would afford **14**,[15] which would yield the regioisomeric side product **7** following reductive elimination. Dissociation of the alkene complex **13** before reinsertion would provide **8**. The *N*-arylated product **5** is presumably formed through C–N bond-forming reductive elimination of **9**.[1] This mechanistic pathway is also consistent with observed ligand effects: ligands that decrease the rate of reductive elimination afford increased amounts of products derived from the proposed intermediate **13**.

Examples of the insertion of alkenes into palladium–nitrogen bonds are rare,[2,16] and only two catalytic reactions that proceed by alkene insertion into a Pd(NRR′)X complex (X = Cl,[16a] $OC(O)C_6F_5$[16b]) have been described.[17–19] The insertion of unactivated alkenes into [Pd(Ar)(NR_2)] complexes has not been reported.

In conclusion, we have developed a new, stereoselective synthesis of pyrrolidines from γ-(*N*-arylamino) alkenes. The transformations described herein are the first examples of catalytic reactions that most likely proceed by the chemoselective intramolecular insertion of an alkene into a [Pd(Ar)(NRR′)] intermediate. Furthermore, the reaction of **4** with 4-bromobiphenyl provides the first probe of the chemoselectivity of insertion under catalytic conditions; the most plausible pathway for the conversion of **4** into **7** and **8** involves olefin insertion into a Pd–N bond. Further studies on the scope, limitations, applications, and mechanism of these reactions are currently underway.

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Keywords: alkene insertion · aryl halides · diastereoselectivity · nitrogen heterocycles · palladium

[1] For reviews on aryl C–N bond-forming reactions that involve Pd(Ar)(NR_2) intermediates, see: a) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *291*, 131–209; b) J. F. Hartwig, *Pure Appl. Chem.* **1999**, *71*, 1417–1423.

[2] a) J. M. Boncella, L. A. Villanueva, *J. Organomet. Chem.* **1994**, *465*, 297–304; b) L. A. Villanueva, K. A. Abboud, J. M. Boncella, *Organometallics* **1992**, *11*, 2963–2965.

[3] For related studies on the synthesis of tetrahydrofurans, see: J. P. Wolfe, M. A. Rossi, *J. Am. Chem. Soc.* **2004**, *126*, 1620–1621.

[4] a) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435–446; b) J. R. Lewis, *Nat. Prod. Rep.* **2001**, *18*, 95–128.

[5] a) A. Mitchinson, A. Nadin, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2862–2892; b) M. Pichon, B. Figadere, *Tetrahedron: Asymmetry* **1996**, *7*, 927–964.

[6] For pyrrolidine syntheses that involve intramolecular C–N bond formation and intermolecular C–C bond formation, see: a) Y. Tamaru, M. Kimura, *Synlett* **1997**, 749–757; b) Y. Tamaru, M. Hojo, Z.-i. Yoshida, *J. Org. Chem.* **1988**, *53*, 5731–5741; c) H. Yorimitsu, K. Wakabayashi, H. Shinokubo, K. Oshima, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1963–1970; d) R. C. Larock, H. Yang, S. M. Weinreb, R. J. Herr, *J. Org. Chem.* **1994**, *59*, 4172–4178.

[7] Imine side products presumably formed through β-hydride elimination of an intermediate [Pd(Ar)(NR_2)] complex are occasionally observed; see reference [1].

[8] G. Fournet, G. Balme, J. Gore, *Tetrahedron* **1990**, *46*, 7763–7774.

[9] Diastereomeric ratios were determined by ^{1}H NMR spectroscopy and/or GC analysis of the crude reaction mixture. The stereochemistry of the products was assigned on the basis of ^{1}H NMR NOE experiments and/or by analogy with related compounds of known configuration.

[10] The reaction of 2-bromonaphthalene with *N*-(4-methoxyphenyl)-3-pentenylamine under the standard reaction conditions afforded only the product of N-arylation; no cyclized products were observed. This result suggests that the regioisomeric products are not formed through initial isomerization of the alkene substrate followed by 5-endocyclization.

[11] ^{1}H NMR spectroscopic analysis of the reaction mixture showed that the products **5**, **6**, **7**, and **8** were formed in a ratio of 6:7:2:1. The use of dppe as a ligand led to a 2:1:2:4 ratio of **5**/**6**/**7**/**8**, and the use of dppb as a ligand afforded a 2:2:2:1 mixture of **5**/**6**/**7**/**8**.

[12] The ligands dppe and dppb have been shown to decrease the rate of C–C and C–N bond-forming reductive elimination and increase the formation of side products by competing β-hydride elimination; see: a) A. Gillie, J. K. Stille, *J. Am. Chem. Soc.* **1980**, *102*, 4933–4941; b) M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 8232–8245; c) J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1144–1157.

[13] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066.

[14] D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1979**, *101*, 4981–4991.

[15] H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2056 – 2057.
[16] a) J. Helaja, R. Göttlich, *Chem. Commun.* **2002**, 720 – 721; b) H. Tsutsui, K. Narasaka, *Chem. Lett.* **1999**, 45 – 46
[17] The treatment of *trans*-[PdH(NHPh)($P(C_6H_{11})_3$)$_2$] with ethylene or acrylonitrile led to reductive elimination of aniline rather than alkene insertion: A. L. Seligson, R. L. Cowan, W. C. Trogler, *Inorg. Chem.* **1991**, *30*, 3371 – 3381.
[18] For examples of insertion reactions of activated alkenes into platinum–nitrogen bonds, see: a) R. L. Cowan, W. C. Trogler, *Organometallics* **1987**, *6*, 2451 – 2453; b) R. L. Cowan, W. C. Trogler, *J. Am. Chem. Soc.* **1989**, *111*, 4750 – 4761.
[19] For an example of a catalytic reaction that proceeds through the insertion of norbornene into an iridium–nitrogen bond, see: A. L. Casalnuovo, J. C. Calabrese, D. Milstein, *J. Am. Chem. Soc.* **1988**, *110*, 6738 – 6744.

