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# Synthesis and Reactivity of Azapalladacyclobutanes

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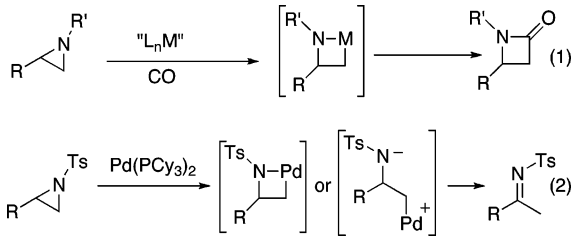
***Abstract:*** *N*-Sulfonyl aziridines undergo oxidative addition to palladium(0) complexes generated in situ from mixtures of $Pd_2(dba)_3$ and 1,10-phenanthroline. The resulting azapalladacyclobutane complexes undergo intramolecular carbopalladation in the presence of copper(I) iodide to afford azapalladabicyclo-[3.2.1]octanes. A deuterium-labeling experiment indicates that the oxidative addition proceeds via $S_N2$-type attack of palladium(0) on the less-hindered carbon of the aziridine ring and that alkene insertion occurs in a syn fashion. The azapalladabicyclo[3.2.1]octane complexes undergo oxidative palladium−carbon bond functionalization in the presence of copper(II) bromide.

## Introduction

The oxidative addition of aziridines to late transition metal complexes has been implicated as a key step in a number of useful metal-catalyzed reactions. For example, transition metal-catalyzed carbonylations of unactivated aziridines have been employed for the construction of $\beta$-lactams (eq 1),[1−7] and the Pd-catalyzed isomerization of *N*-tosylaziridines to *N*-tosyl-ketimines is also believed to proceed via oxidative addition of




an aziridine to Pd(0) (eq 2).[8] In some instances azametallacyclobutanes that derive from oxidative addition of aziridines to low-valent late transition metal complexes have been invoked as plausible intermediates in these transformations,[1,2] although experimental evidence for these species is limited.

In addition to the established transformations described above, azametallacyclobutanes could potentially serve as intermediates in metal-catalyzed [3 + 2] coupling reactions between aziridines and alkenes that would afford substituted pyrrolidine products.[9] As shown in Scheme 1, oxidative addition of an aziridine to a metal complex could generate azametallacyclobutane **1**, which could undergo insertion of an alkene into either the M−N bond[10,11] to afford **2** or the M−C bond[12,13] to provide **3**. Subsequent C−C[14] or C−N[15,16] bond-forming reductive elimination of **2** or **3**, respectively, would give a pyrrolidine product (**4**). However, several of the key steps in this process are

(1) For examples of reactions employing rhodium catalysts see: (a) Alper, H.; Urso, F.; Smith, D. J. H. *J. Am. Chem. Soc.* **1983**, *105*, 6737−6738. (b) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931−934. (c) Khumtaveeporn, K.; Alper, H. *Acc. Chem. Res.* **1995**, *28*, 414−422. (d) Lu, S.-M.; Alper, H. *J. Org. Chem.* **2004**, *69*, 3558−3561.

(2) For examples of reactions employing cobalt catalysts see: (a) Piotti, M. E.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 111−116. (b) Davoli, P.; Moretti, I.; Prati, F.; Alper, H. *J. Org. Chem.* **1999**, *64*, 518−521. (c) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem. Int. Ed.* **2002**, *41*, 2781−2784.

(3) For palladium-catalyzed carbonylations of methyleneaziridines see: Alper, H.; Hamel, N. *Tetrahedron Lett.* **1987**, *28*, 3237−3240.

(4) For a stoichiometric nickel-mediated aziridine carbonylation see: Chamchaang, W.; Pinhas, A. R. *J. Org. Chem.* **1990**, *55*, 2943−2950.

(5) For related carboxylations and carbonylations of unactivated epoxides see: (a) De Pasquale, R. J. *J. Chem. Soc., Chem. Commun.* **1973**, 157−158. (b) Kamiya, Y.; Kawato, K.; Ohta, H. *Chem. Lett.* **1980**, 1549−1552. (c) Ref 1c. (d) Ref 2c. (e) Lee, J. T.; Thomas, P. J.; Alper, H. *J. Org. Chem.* **2001**, *66*, 5424−5426. (f) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1174−1175. (g) Schmidt, J. A. R.; Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Org. Lett.* **2004**, *6*, 373−376. (h) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *Pure Appl. Chem.* **2004**, *76*, 557−564. (i) Schmidt, J. A. R.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2005**, *127*, 11426−11435.

(6) Several Lewis acid-catalyzed cycloadditions of aziridines and heterocumulenes employing palladium(II) complexes have been reported. See: (a) Baeg, J.-O.; Alper, H. *J. Org. Chem.* **1992**, *57*, 157−162. (b) Baeg, J.-O.; Bensimon, C.; Alper, H. *J. Am. Chem. Soc.* **1995**, *117*, 4700−4701. (c) Maas, H.; Bensimon, C.; Alper, H. *J. Org. Chem.* **1998**, *63*, 17−20.

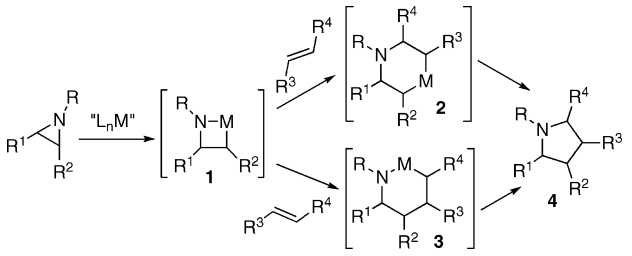
(7) 2-Vinylaziridines, which are activated for oxidative addition, have also been shown to undergo palladium-catalyzed insertions of carbon monoxide, isocyanates, phenyl isothiocyanate, carbodiimides, and alkylidene malonates. These reactions are believed to proceed via intermediate allylpalladium complexes. See: (a) Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887−5890. (b) Dong, C.; Alper, H. *Tetrahedron: Asymmetry* **2004**, *15*, 1537−1540. (c) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836−11837. (d) Trost, B. M.; Fandrick, D. R. *Org. Lett.* **2005**, *7*, 823−826. (e) Spears, G. W.; Nakanishi, K.; Ohfune, Y. *Synlett* **1991**, 91−92. (f) Tanner, D.; Somfai, P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2415−2418. (g) Aoyagi, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 5977−5980.

(8) A portion of this work has been previously communicated. See: Wolfe, J. P.; Ney, J. E. *Org. Lett.* **2003**, *5*, 4607−4610.

(9) The synthesis of tetrahydrofuran via Rh-catalyzed insertion of ethylene into ethylene oxide has been previously described, but this reaction has not been demonstrated with other alkenes or epoxides. See: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; pp 640−641.

(10) For examples of olefin or alkyne insertion into isolated transition metal amido complexes see: (a) Cowan, R. L.; Trogler, W. C. *Organometallics* **1987**, *6*, 2451−2453. (b) Cowan, R. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4750−4761. (c) Villanueva, L. A.; Abboud, K. A.; Boncella, J. M. *Organometallics* **1992**, *11*, 2963−2965. (d) VanderLende, D. D.; Abboud, K. A.; Boncella, J. M. *Inorg. Chem.* **1995**, *34*, 5319−5326. (e) Dahlenburg, L.; Herbst, K. *J. Chem. Soc., Dalton Trans.* **1999**, 3935−3939. (f) Zhao, P.; Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 12066−12073.

***Scheme 1***




unprecedented (e.g., the conversion of **1** to **2** or **3**) or have not been thoroughly explored (e.g., the formation of **1** from an aziridine).

Only two studies have examined the synthesis and reactivity of late transition metal azametallacyclobutane complexes that contain an anionic amido group and a saturated backbone (e.g., **1**).[17−22] The first example of the synthesis and isolation of an azametallacyclobutane of this type was reported by Bergman in 1988.[17] The C−H activation of *tert*-butylamine with Cp*-($PMe_3$)$IrH_2$ provided an azairidacyclobutane complex, which was found to undergo insertion of *tert*-butylisocyanide into the Ir−N bond. In the second study, Hillhouse reported that *N*-tosyl-2-alkylaziridines undergo oxidative addition to (bpy)Ni(COD) or (bpy)$NiEt_2$ to afford azanickelacyclobutanes via an $S_N2$ mechanism.[18] Although small-molecule insertion chemistry of the nickel complexes was not reported, treatment with oxygen led to C−N bond-forming reductive elimination that regenerated the substituted aziridines. The experiments described by Hillhouse represent the first and only examples of oxidative addition reactions between aziridines and late transition metal complexes that afford isolable azametallacyclobutane products.

In this Article we describe the first syntheses of azapalladacyclobutane complexes of the general structure **1**,[21,22] which were accomplished through the oxidative addition of aziridines to Pd(0) complexes derived from $Pd_2(dba)_3$ and 1,10-phenathroline (phen). We also demonstrate the unprecedented CuI-catalyzed insertion of alkenes into the azametallacyclobutanes, which occurs in an intramolecular fashion to provide unusual bridged bicyclic palladacycles. The azapalladabicyclo[3.2.1]-octane products of these reactions undergo C−X (X = Br, OAc) bond-forming reductive elimination upon treatment with $CuBr_2$ or $PhI(OAc)_2$ to provide substituted cyclopentylamine derivatives in moderate yield.

## Results

**Oxidative Addition Reactions.** In our preliminary experiments, we sought to examine the synthesis of azapalladacyclobutane complexes via the oxidative addition of aziridines to Pd(0). Palladium was chosen for these studies due to its demonstrated utility in catalytic cross-coupling reactions that involve oxidative addition, small-molecule insertion, and reductive elimination processes. We initially examined the stoichiometric reaction of *N*-tosyl-2-butylaziridine (**5**) with Pd/phosphine complexes or mixtures of $Pd_2(dba)_3$ and phosphine or amine ligands. As shown in Table 1, treatment of **5** with $Pd[PCy_3]_2$ or $Pd[P(t\text{-}Bu)_2Me]_2$ provided *N*-tosylimine **6**, which presumably results from oxidative addition followed by $\beta$-hydride elimination, as the sole detectable product (entries 3 and 4).[23] Interestingly, although no reaction occurred between **5** and mixtures of $Pd_2(dba)_3$/phen (entry 5),[24] subjection of the

(11) For catalytic reactions involving olefin or alkyne insertion into transition metal amido complexes see: (a) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738−6744. (b) Tsutsui, H.; Narasaka, K. *Chem. Lett.* **1999**, 45−46. (c) Kitamura, M.; Zaman, S.; Narasaka, K. *Synlett* **2001**, 974−976. (d) Helaja, J.; Göttlich, R. *Chem. Commun.* **2002**, 720−721. (e) Ney, J. E.; Wolfe, J. P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3605−3608. (f) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447−6459. (g) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644−8651. (h) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893−2901. (i) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868−2869. (j) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179−7181.

(12) For general reviews covering the insertion of olefins into metal−carbon bonds see: (a) Yamamoto, A. *J. Chem. Soc., Dalton Trans.* **1999**, 1027−1037. (b) Yamamoto, A.; Kayaki, Y.; Nagayama, K.; Shimizu, I. *Synlett* **2000**, 925−937. (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

(13) For catalytic reactions involving olefin insertions into metal alkyls bearing $\beta$-hydrogen atoms see: (a) Rix, F. C.; Brookhart, M. *J. Am. Chem. Soc.* **1995**, *117*, 1137−1138. (b) Johnson, L. K.; Killian, C. M.; Brookhart, M. *J. Am. Chem. Soc.* **1995**, *117*, 6414−6415. (c) Gottfried, A. C.; Brookhart, M. *Macromolecules* **2001**, *34*, 1140−1142. (d) Oh, C. H.; Rhim, C. Y.; Kang, J. H.; Kim, A.; Park, B. S.; Seo, Y. *Tetrahedron Lett.* **1996**, *37*, 8875−8878. (e) Schweizer, S.; Song, Z.-Z.; Meyer, F. E.; Parsons, P. J.; De Meijere, A. *Angew. Chem. Int. Ed.* **1999**, *38*, 1452−1454. (f) Quan, L. G.; Cha, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 12424−12425. (g) Widenhoefer, R. A. *Acc. Chem. Res.* **2002**, *35*, 905−913 and references therein. (h) Perch, N. S.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 6332−6346.

(14) (a) Cardenas, D. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3018−3020. (b) Cardenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384−387. (c) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187−3204. (d) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525−1532. (e) Netherton, M. R.; Fu, G. C. *Top. Organomet. Chem.* **2005**, *14*, 85−108.

(15) Catalytic reactions involving C($sp^2$)−N bond-forming reductive elimination are well-known. For reviews see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131−209. (b) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417−1423. (c) Barluenga, J.; Valdes, C. *Chem. Commun.* **2005**, 4891−4901.

(16) Reductive elimination reactions that form C($sp^3$)−N bonds are rare and often require oxidative conditions; for examples see: (a) Bäckvall, J.-E. *Tetrahedron Lett.* **1978**, *19*, 163−166. (b) Koo, K.; Hillhouse, G. L. *Organometallics* **1995**, *14*, 4421−4423. (c) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250−11251. (d) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muniz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586−14587. (e) Ref 11i.

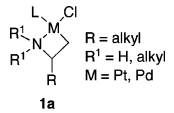
(17) Klein, D. P.; Hayes, J. C.; Bergman, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 3704−3706.

(18) Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890−2891.

(19) The oxidative addition of ethyleneimine to $K_2PtCl_4$ in aqueous HCl has been reported to afford $KPt(CH_2CH_2N^+H_3)Cl_5$. See: Mitchenko, S. A.; Slinkin, S. M.; Vdovichenko, A. N.; Zamashchikov, V. V. *Metallorg. Khim.* **1991**, *4*, 1031−1035.

(20) For a discussion of the synthesis and reactivity of oxymetallacyclobutanes of Rh, Ir, Pt, and Ru see: (a) Schlodder, R.; Ibers, J. A.; Lenarda, M.; Graziani, M. *J. Am. Chem. Soc.* **1974**, *96*, 6893−6900. (b) Lenarda, M.; Ros, R.; Traverso, O.; Pitts, W. D.; Baddley, W. H.; Graziani, M. *Inorg. Chem.* **1977**, *16*, 3178−3182. (c) Zlota, A. A.; Frolow, F.; Milstein, D. *J. Am. Chem. Soc.* **1990**, *112*, 6411−6413. (d) Calhorda, M. J.; Galvao, A. M.; Unaleroglu, C.; Zlota, A. A.; Frolow, F.; Milstein, D. *Organometallics* **1993**, *12*, 3316−3325. (e) Hartwig, J. F.; Bergman, R. G.; Andersen, R. A. *Organometallics* **1991**, *10*, 3326−3344. (f) Hartwig, J. F.; Bergman, R. G.; Andersen, R. A. *Organometallics* **1991**, *10*, 3344−3362.

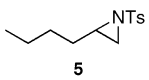
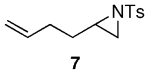
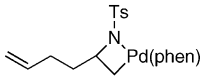
(21) Azapalladacyclobutanes and azaplatinacyclobutanes that contain a neutral amino group with the general structure **1a** have been prepared via aminopalladation or aminoplatination of alkenes. See: (a) Briggs, J. R.; Crocker, C.; McDonald, W. S.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1981**, 575−580. (b) Green, M.; Sarhan, J. K. K.; Al-Najjar, I. M. *Organometallics* **1984**, *3*, 520−524 and references therein. (c) De Renzi, A.; Di Blasio, B.; Morelli, G.; Vitagliano, A. *Inorg. Chim. Acta* **1982**, *63*, 233−241. (d) Åkermark, B.; Zetterberg, K. *J. Am. Chem. Soc.* **1984**, *106*, 5560−5561. (e) Hegedus, L. S.; Åkermark, B.; Zetterberg, K.; Olsson, L. F. *J. Am. Chem. Soc.* **1984**, *106*, 7122−7126. (f) Arnek, R.; Zetterberg, K. *Organometallics* **1987**, *6*, 1230−1235. (g) Zhang, L.; Zetterberg, K. *Organometallics* **1991**, *10*, 3806−3813.




**1a**

(22) For examples of four-membered platinalactam and palladalactam complexes see: (a) Henderson, W.; Oliver, A. G.; Nicholson, B. K. *Inorg. Chim. Acta* **2000**, *298*, 84−89. (b) Henderson, W.; Nicholson, B. K.; Oliver, A. G. *J. Chem. Soc., Dalton Trans.* **1994**, 1831−1835. (c) Henderson, W.; Fawcett, J.; Kemmitt, R. D. W.; Proctor, C.; Russell, D. R. *J. Chem. Soc., Dalton Trans.* **1994**, 3085−3090.

***Table 1.*** Ligand Effects[a]

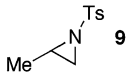
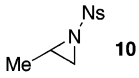
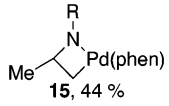
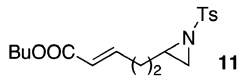
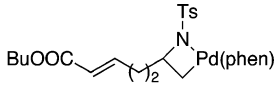
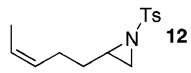
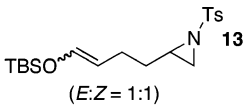
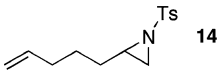
| Entry | Aziridine | Metal Complex | Product |
|---|---|---|---|
| 1 |  **5** | $Pd_2(dba)_3$/ $P(o\text{-tol})_3$ | No Reaction |
| 2 | | $Pd[P(t\text{-Bu})_3]_2$ | No Reaction |
| 3 | | $Pd[P(t\text{-Bu})_2Me]_2$ |  **6** |
| 4 | | $Pd[PCy_3]_2$ |  **6** |
| 5 | | $Pd_2(dba)_3$/ Phen | No Reaction |
| 6 |  **7** | $Pd_2(dba)_3$/ Phen |  **8**, 45 % |
| 7 | | $Pd_2(dba)_3$/ bpy | No Reaction |
| 8 | | $Pd_2(dba)_3$/ 5-nitro-Phen | No Reaction |
| 9 | | $Pd[PCy_3]_2$ | Complex Mixture |
| 10 | | $Pd_2(dba)_3$/ dppe | No Reaction |
| 11 | | $Pd_2(dba)_3$/ dcpe | No Reaction |
| 12 | | $Pd_2(dba)_3$/ dppf | No Reaction |

[a] Conditions: 1.0−1.5 equiv aziridine, 0.5 equiv $Pd_2(dba)_3$ (1.0 equiv Pd), 2.0 equiv monodentate ligands, 1.0 equiv bidentate ligands, THF or $C_6D_6$ (0.01 M in Pd), 65−70 °C.

unsaturated *N*-tosyl-2-but-3-enylaziridine **7** to these conditions afforded azametallacyclobutane **8** in 45% isolated yield as an air-stable yellow solid (entry 6). The structure of metallacycle **8**, which results from oxidative addition of the less-hindered C−N bond in **7** to palladium(0), was established through $^1$H NMR, $^{13}$C NMR, COSY, IR, and HRMS analysis. Efforts to prepare the analogous azapalladacyclobutane complex bearing $PCy_3$ ligands from **7** and $Pd[PCy_3]_2$ provided complex mixtures of products (entry 9); neither the desired metallacycle nor 2-(toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane[25] (the product that would result from oxidative addition, alkene insertion, and reductive elimination as described in Scheme 1) was observed. The oxidative addition of **7** failed to proceed when the bisphosphines dppe, dppf, and dcpe were employed as ligands (entries 10−12).[24] Surprisingly, bpy[24] was also not an effective ligand for the oxidative addition of **7**; the aziridine was recovered unchanged from this reaction (entry 7).

To assess the scope and limitations of this oxidative addition reaction, a series of *N*-sulfonylaziridine substrates (**9**−**14**) was prepared and treated with mixtures of $Pd_2(dba)_3$ and phen. As shown in Table 2, *N*-tosylaziridines lacking a tethered olefin, such as **9**, were inert to the reaction conditions (entry 1). In

***Table 2.*** Synthesis of Azapalladacyclobutanes from *N*-Sulfonylaziridines and $Pd^0$/Phen[a,b]

| Entry | Aziridine | Product |
|---|---|---|
| 1 |  **9** | No rxn |
| 2 |  **10** |  **15**, 44 % |
| 3 |  **11** |  **16**, 44 % |
| 4 |  **12** | No rxn |
| 5 |  **13** (*E*:*Z* = 1:1) | No rxn |
| 6 |  **14** | No Rxn |

[a] Conditions: 1.0−1.5 equiv aziridine, 0.5 equiv $Pd_2(dba)_3$ (1.0 equiv Pd), 1.0 equiv phen, THF (0.01 M in Pd), 65 °C. [b] Ns = 4-nitrobenzenesulfonyl.

contrast, the reaction of 2-methylaziridine derivative **10**, which bears a more strongly activating *N*-nosyl substituent (nosyl = 4-nitrophenylsulfonyl)[26] afforded metallacycle **15** in 44% isolated yield (entry 2). The reactivity of the aziridine substrates toward oxidative addition to Pd(0) was dependent on both the steric and electronic properties of the tethered alkene. For example, aziridine **11**, which bears an electron-deficient internal olefin, underwent facile oxidative addition to afford **16** (entry 3). However, aziridine substrates bearing internal alkenes substituted with a methyl group (**12**) or a silyloxy group (**13**) did not react (entries 4 and 5). The reactivity of the aziridine toward Pd/phen was also dependent on the length of the tether between the alkene and the aziridine. The butenyl-containing substrate **7** underwent clean oxidative addition to Pd(0) (Table 1, entry 6), but no reaction was observed between the Pd/phen mixture and pentenyl-substituted aziridine **14** (Table 2, entry 6).

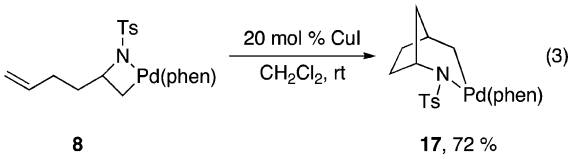
**Olefin Insertion Reactions of Azapalladacyclobutane Complexes.** With azapalladacyclobutane complexes **8**, **15**, and **16** in hand, we sought to develop conditions that would effect intramolecular migratory insertion of the tethered olefin. Metallacycle **8** failed to undergo intramolecular olefin insertion when heated to temperatures up to 70 °C in a variety of solvents including benzene, chlorobenzene, DME, acetonitrile, and DMSO. However, treatment of a methylene chloride solution of **8** with a catalytic amount of copper(I) iodide resulted in clean intramolecular carbopalladation of the alkene to provide bridged bicyclic complex **17** in 72% yield as an air-stable orange solid (eq 3).[27] Analysis of **17** by $^1$H NMR, $^{13}$C NMR, COSY, HSQC, difference NOE, IR, and HRMS confirmed the structure shown below.

(23) Control experiments demonstrated that the aziridine did not isomerize when heated for 15 h at 70 °C in $C_6D_6$ with 1 equiv of tricyclohexylphosphine in the absence of Pd.

(24) Phen = 1,10-phenanthroline, dppe = 1,2-bis(diphenylphospino)ethane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, dppb = 1,4-bis(diphenylphosphino)butane, dcpe = 1,2-bis(dicyclohexylphosphino)ethane, bpy = 2,2′-bipyridine.

(25) Heesing, A.; Herdering, W. *Chem. Ber.* **1983**, *116*, 1081−1096.

(26) Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253−5256.

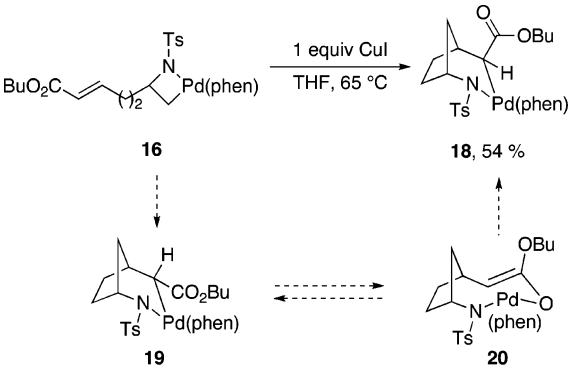



**8** **17**, 72 %

Treatment of **8** with several other late transition metal salts, including gold(I) chloride, palladium(II) acetate, and zinc(II) iodide, provided detectable amounts of **17**. However, these transformations were more sluggish and/or less clean than the CuI-catalyzed process. Use of other copper salts such as CuBr or CuCl gave results similar to those obtained with CuI. Treatment of **8** with sodium iodide or tetrabutylammonium iodide did not lead to any observable reaction, which suggests that the insertion is facilitated by a soft Lewis acid rather than a halide or other anionic species.

Intramolecular carbopalladation of metallacycle **16** required more forcing conditions than were employed for the transformation of **8** to **17**;[28] complete conversion of **16** to C-bound palladium enolate **18** was achieved using a stoichiometric amount of CuI at 65 °C (Scheme 2). The bicyclic complex **18** was obtained as a single stereoisomer, which was determined to contain a C-bound enolate and exo orientation of the ester substituent, through $^{13}$C NMR and NOE analysis, respectively. This stereochemical outcome corresponds to apparent syn carbopalladation of the *E*-olefin in **16**. However, initial formation of the endo isomer **19** followed by conversion to **18** via O-bound enolate **20** could not be unambiguously ruled out in this system.[29,30] Subsequent deuterium-labeling experiments confirmed that alkene insertion most likely occurs through a syn carbopalladation pathway (see below).

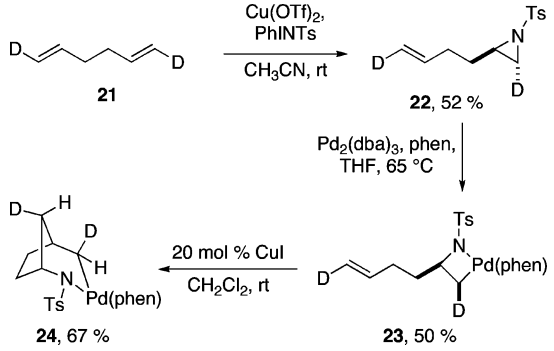
***Scheme 2***




Although **8** and **16** were found to undergo intramolecular Cu-catalyzed olefin insertion, efforts to induce intermolecular olefin insertion with a variety of different alkenes were unsuccessful. Similarly, metallacycle **15**, which is derived from *N*-nosyl-2-methylaziridine (**10**), also failed to participate in intermolecular insertion reactions with a variety of olefins, including 1-decene, styrene, and butyl acrylate. Reactions were conducted in both methylene chloride and THF, with and without added CuI.

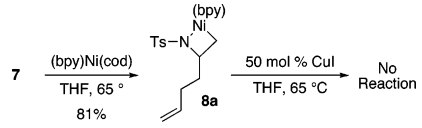
**Stereochemistry of Oxidative Addition and Olefin Insertion.** To explore the mechanistic details of the oxidative addition and olefin insertion reactions described above, (*E*,*E*)-1,6-$d^2$-1,5-hexadiene (**21**)[31] (obtained with ca. 5:1 *E*/*Z* selectivity) was subjected to Evans aziridination conditions[32] to generate an *N*-tosyl-2-(but-3-enyl)aziridine (**22**) that was stereoselectively and regioselectively deuterated at C1 and C6 (Scheme 3). This material was obtained as a 5:1 mixture of trans/cis aziridines and a ca. 5:1 mixture of alkene isomers. Oxidative addition of **22** to Pd(0)/phen afforded azapalladacyclobutane **23** as a 5:1 mixture of cis/trans metallacycles and a 5:1 mixture of alkene isomers. Thus, the oxidative addition occurs with clean inversion of configuration at the reacting methylene carbon. Treatment of azametallacyclobutane **23** with a catalytic amount of CuI in methylene chloride afforded **24**, the product of intramolecular syn carbopalladation, as a 5:1 mixture of C3 epimers and a 5:1 mixture of C8 epimers.[33]

***Scheme 3***




The stereochemistry of azapalladacyclobutane **23** was established through two-dimensional $^1$H NMR analysis of the all-proteo analogue **8**. The proton resonances observed at $\delta$ 4.51−4.45, 1.12, and 0.57 ppm were assigned to $H_A$, $H_B$, and $H_C$, respectively, through COSY analysis. A cross-peak between the resonances attributed to $H_A$ and $H_B$ was observed in the 2D-NOESY spectrum of **8**, which established the cis relationship between these protons. The $^1$H NMR spectrum of **23** lacked

(27) Azanickelacyclobutane **8a**, which was prepared from **7** using Hillhouse's conditions, did not undergo intramolecular alkene insertion under thermal or Cu-mediated conditions.




(28) Insertion reactions of internal alkenes are usually slower than insertion reactions of terminal alkenes. For selected examples see: (a) Gürtler, C.; Buchwald, S. L. *Chem.—Eur. J.* **1999**, *5*, 3107−3112. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000.

(29) For an example of partial stereochemical scrambling at the palladium-bound carbon in a C-bound palladium enolate see: Lu, G.; Malinakova, H. C. *J. Org. Chem.* **2004**, *69*, 8266−8279.

(30) For examples of O-bound palladium enolate complexes see: (a) Ito, Y.; Nakatsuka, M.; Kise, N.; Saegusa, T. *Tetrahedron Lett.* **1980**, *21*, 2873−2876. (b) Bouaoud, S. E.; Braunstein, P.; Grandjean, D.; Matt, D.; Nobel, D. *J. Chem. Soc., Chem. Commun.* **1987**, 488−490. (c) Bouaoud, S.-E.; Braunstein, P.; Grandjean, D.; Matt, D.; Nobel, D. *Inorg. Chem.* **1988**, *27*, 2279−2286. (d) Andrieu, J.; Braunstein, P.; Dusausoy, Y.; Ghermani, N. E. *Inorg. Chem.* **1996**, *35*, 7174−7180. (e) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463−466. (f) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816−5817. (g) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398−3416. (h) Braunstein, P. *Chem. Rev.* **2006**, *106*, 134−159.

(31) Piers, W. E.; Bercaw, J. E. *J. Am. Chem. Soc.* **1990**, *112*, 9406−9407.

(32) Evans, D. A.; Bilodeau, M. T.; Faul, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 2742−2753.

(33) See the Supporting Information for copies of the $^1$H NMR spectra obtained for **8**, **17**, **18**, **22**, **23**, and **24** along with selected 2D NMR spectra for **8**, **17**, and **18**.

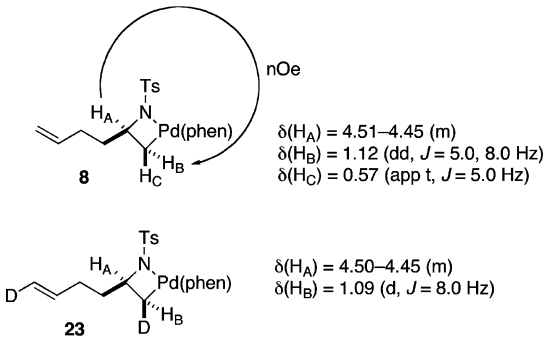



***Figure 1.***

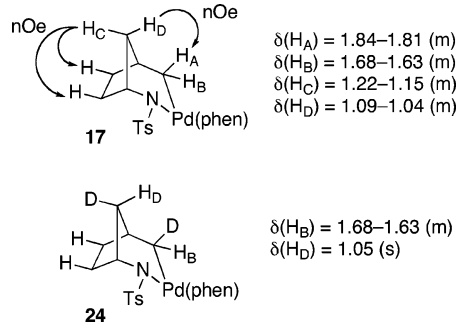
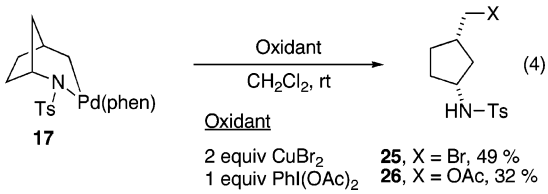



***Figure 2.***

the resonance at $\delta$ 0.57, which is consistent with the structure shown in Figure 1.[33]

The stereochemistry of **24** was established in a similar fashion. The resonances in the $^1$H NMR spectrum of **17** were assigned on the basis of COSY, HSQC, and difference NOE spectroscopy as shown in Figure 2. The $^1$H NMR spectrum of **24** lacked the resonances attributable to $H_A$ and $H_C$, establishing the stereochemical configuration of this complex.

**Reactivity of Bicyclic Palladium Complex 17.** Having prepared azapalladabicyclo[3.2.1]octane derivatives **17** and **18**, we sought to probe whether these complexes could be induced to undergo C−N bond-forming reductive elimination to generate azanorbornane products under thermal or oxidative conditions.[16] No reaction was observed when a solution of **17** in toluene-$d_8$ was heated to 120 °C. However, treatment of **17** with 2 equiv of copper(II) bromide afforded a 49% isolated yield of **25**, the product of carbon−bromine bond formation (eq 4).[34] Similarly, treatment of **17** with 1 equiv of $PhI(OAc)_2$ provided acetate **26** in 32% yield.[35] The use of other oxidants resulted in the formation of complex mixtures of products (*m*-CPBA) or failed to promote any reaction (oxone, $O_2$). Complex **17** was also unreactive toward intermolecular insertion of alkenes or alkynes, including 1-decene and diethyl acetylenedicarboxylate. Treatment of **18** with $CuBr_2$ afforded a complex mixture of products.[36]

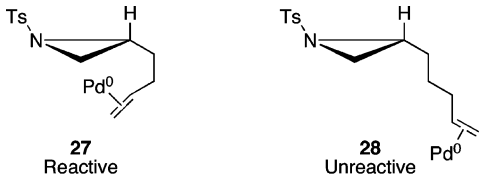



## Discussion

**Oxidative Addition of Aziridines to Pd(0).** The reactivity of *N*-sulfonyl aziridines toward Pd(0) complexes is highly dependent on two structural features of the aziridine moiety: sterics and electrophilicity. In all cases examined (Tables 1 and 2), oxidative addition occurred exclusively via attack on the less-substituted carbon of the aziridine, and sterically bulky 1,1- or 1,2-disubstituted aziridines were unreactive. Use of a more electron-deficient group on the nitrogen atom led to increased reactivity as demonstrated by the observation that the more electrophilic *N*-nosyl-2-methylaziridine (**10**) readily undergoes oxidative addition to $Pd_2(dba)_3$/phen, whereas *N*-tosyl-2-methylaziridine (**9**) is unreactive under these conditions (Table 2).

The presence of a tethered alkene also facilitates the oxidative addition reaction. For example, *N*-tosyl-2-but-3-enylaziridine **7** undergoes oxidative addition to $Pd_2(dba)_3$/phen, whereas *N*-tosyl-2-butylaziridine **5** does not. One possible explanation for this effect is that precoordination of the tethered olefin to palladium(0) facilitates chelate-directed oxidative addition to the aziridine (Scheme 4, **27**).[37] The relative reactivities of

***Scheme 4***




internal olefin-containing substrates **11**−**13** are consistent with this model. Electron-deficient olefins are known to bind strongly to palladium(0).[38] Accordingly, acrylate-containing aziridine **11** underwent oxidative addition to form **16** (Table 2, entry 3).[39] Electron-rich internal olefins, in contrast to terminal and electron-deficient internal alkenes, bind weakly to palladium(0).[38] As a result, **12** and **13** were inert to the reaction conditions (Table 2, entries 4 and 5). The length of the tether between the aziridine and the olefin also affected the reactivity of the azirdine

(34) (a) Henry, P. M. *J. Org. Chem.* **1967**, *32*, 2575−2580. (b) Henry, P. M. *J. Org. Chem.* **1974**, *39*, 3871−3874 and references therein. (c) Budnik, R. A.; Kochi, J. K. *J. Organomet. Chem.* **1976**, *116*, C3−C6. (d) Bäckvall, J.-E. *Tetrahedron Lett.* **1977**, *18*, 467−468. (e) Bäckvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335−342. (f) Zhu, G.; Ma, S.; Lu, X.; Huang, Q. *J. Chem. Soc., Chem. Commun.* **1995**, 271−273 and references therein.

(35) (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542−9543. (b) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790−12791 and references therein.

(36) The major products appear to be two α-bromoester stereoisomers that would result from oxidative bromination of **18** in a manner analogous to **17**. These assignments were made on the basis of $^1$H NMR and COSY analysis of an inseparable mixture of the two stereoisomers that was contaminated with ca. 20% of an unidentified impurity. A third product that was isolated in small quantities (ca. 5%) has tentatively been assigned on the basis of $^1$H NMR and COSY analysis to be an α,β-unsaturated ester that would derive from loss of HBr from the α-bromoester. Small amounts of several other unidentified products were also observed.

(37) For an example of chelation-assisted oxidative addition of an alkyl chloride to Pd(0), see: Portnoy, M.; Ben-David, Y.; Milstein, D. *J. Organomet. Chem.* **1995**, *503*, 149−153.

(38) (a) Ozawa, F.; Ito, T.; Nakamura, Y.; Yamamoto, A. *J. Organomet. Chem.* **1979**, *168*, 375−391. (b) Canovese, L.; Visentin, F.; Uguagliati, P.; Crociani, B. *J. Chem. Soc., Dalton Trans.* **1996**, 1921−1926. (c) Stahl, S. S.; Thorman, J. L.; de Silva, N.; Guzei, I. A.; Clark, R. W. *J. Am. Chem. Soc.* **2003**, *125*, 12−13. (d) Popp, B. V.; Thorman, J. L.; Morales, C. M.; Landis, C. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 14832−14842.

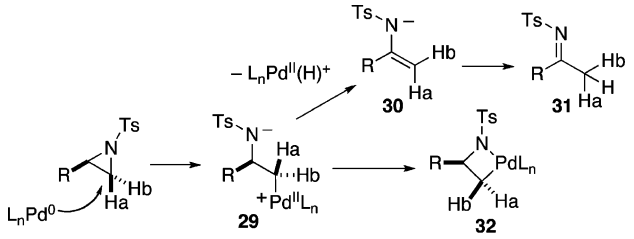
(39) In our system, the ability of the alkene to bind to Pd(0) appears to override the tendency of electron-poor alkenes to decrease the reactivity of Pd(0) complexes in oxidative addition reactions. See: (a) Amatore, C.; Carre, E.; Jutand, A.; Medjour, Y. *Organometallics* **2002**, *21*, 4540−4545. (b) Scrivanti, A.; Beghetto, V.; Matteoli, U.; Antonaroli, S.; Marini, A.; Crociani, B. *Tetrahedron* **2005**, *61*, 9752−9758.

substrates. The two-carbon tether present in **7**, which would lead to nucleophilic attack via a six-membered chelate, led to good reactivity (Scheme 4, **27**). However, the three-carbon tether present in **14** did not promote reactivity via a seven-membered chelate (Scheme 4, **28**).

The ability of Pd(0) complexes to undergo oxidative addition to *N*-sulfonylaziridines also appears to be dependent on both the steric and electronic properties of the metal complex. For example, *N*-tosyl-2-but-3-enylaziridine **7** undergoes addition to $Pd_2(dba)_3$/phen but not to the complex generated from $Pd_2(dba)_3$ and the less electron-rich 5-nitro-phen (Table 1, entry 8). A similar electronic effect is observed in the conversion of *N*-tosyl-2-butylaziridine **5** to *N*-tosylketimine **6** via oxidative addition followed by $\beta$-hydride elimination. The reaction is facilitated by the electron-rich Pd(0) complexes $Pd[PCy_3]_2$ and $Pd[P(t\text{-}Bu_2)Me]_2$, but no reaction is observed with the less nucleophilic $Pd_2(dba)_3$/$P(o\text{-}tol)_3$ mixture (Table 1, entry 1). Use of very bulky Pd complexes (e.g., $Pd[P(t\text{-}Bu)_3]_2$) also inhibits oxidative addition (Table 1, entry 2); the steric bulk of the complex presumably hinders approach of the metal to the electrophile.

The results described above are most consistent with a mechanism for oxidative addition that involves a nucleophilic $S_N2$-type attack of the Pd(0) complex on the aziridine. This nucleophilic attack would initially generate a zwitterionic intermediate (**29**) that can react further via one of two pathways (Scheme 5). Intermediate **29** can undergo a $\sigma$-bond rotation followed by nucleophilic attack of the anionic sulfonamide nitrogen on the cationic palladium center to generate azametallacyclobutane **32**, or it can undergo $\beta$-hydride elimination to provide anionic enamine **30**, which is protonated to generate an *N*-tosylimine (**31**).[8] This mechanistic hypothesis is supported by the observed inversion of configuration in the oxidative addition of deuterated aziridine **22** to $Pd_2(dba)_3$/phen, which is consistent with $S_N2$ substitution.

***Scheme 5***

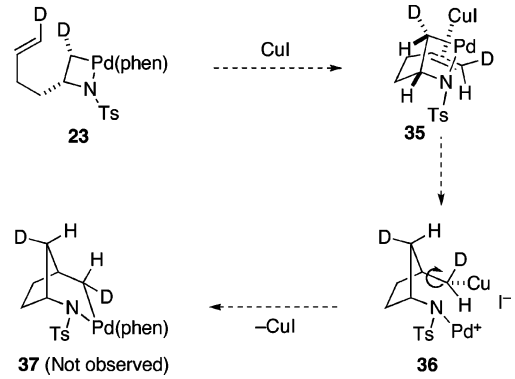



The structural features of the metal complex have a large impact on the nature of the products that are isolated from the oxidative addition reactions. This effect is presumably a reflection of the stability of intermediate **29** toward $\beta$-hydride elimination and/or its reactivity toward ring closure. The electron-rich monodentate phosphine ligands $PCy_3$ and $P(t\text{-}Bu)_2Me$ are sufficiently reactive to promote the oxidative addition of *N*-tosylaziridines without the requirement for precomplexation to a tethered alkene on the substrate, but the resulting intermediate **29** is unstable and is ultimately converted to the *N*-tosylimine (**31**). In contrast, the complex derived from mixtures of $Pd_2(dba)_3$/phen is less reactive, and chelation assistance is required to facilitate oxidative addition. However, the resulting intermediate **29** is sufficiently stable toward $\beta$-hydride elimination to allow for $\sigma$-bond rotation and capture by the sulfonamide group to afford the azametallacyclobutane (**32**).

**Intramolecular Alkene Insertion of Azapalladacyclobutane Complexes.** Azapalladacyclobutanes **8** and **16** undergo intramolecular syn carbopalladation of the pendant alkene to provide the unusual azapalladabicyclo[3.2.1]octane derivatives **17** and **18**. Reactivity toward alkene insertion is only observed in the presence of soft Lewis acids, with optimal results obtained using added CuI. These reactions are the first examples of olefin insertion into azametallacyclobutane complexes, and to the best of our knowledge, they are also the first reported instances in which an added metal salt facilitates the migratory insertion of an alkene into a Pd−C bond.

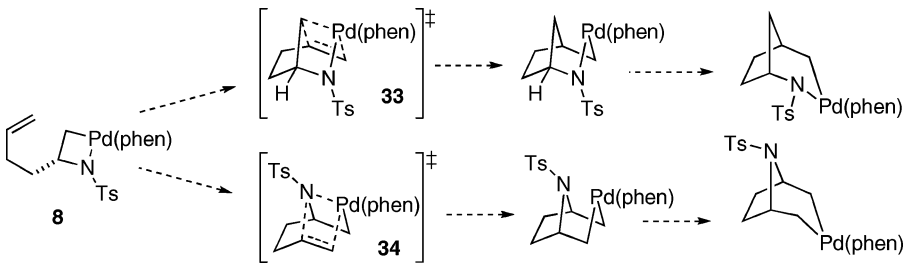
The direct, uncatalyzed insertion of the alkene into the azametallacyclobutane was not observed. This lack of reactivity under thermal conditions may be due to the anti-Bredt character of the transition state for insertion. As shown in Scheme 6, insertion of the alkene into either the Pd−C or Pd−N bond of **8** would proceed via transition state **33** or **34**, respectively. Both transition states contain partial double bond character between a bridgehead atom and the adjacent C2 atom. These transition states would likely be high in energy; thus, low reactivity is observed.

***Scheme 7***

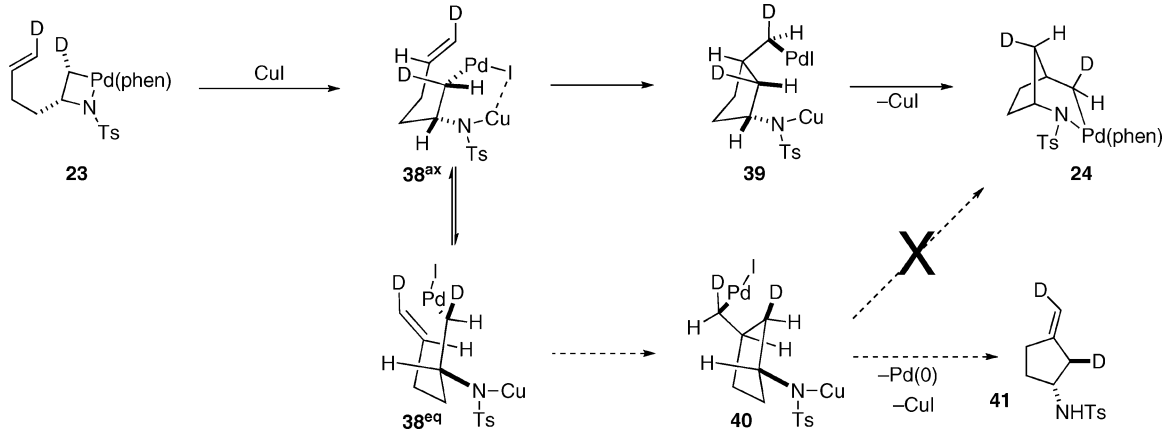



The unexpected effect of copper on this otherwise unfavorable olefin insertion reaction could arise from two plausible scenarios, which can be distinguished by analysis of the insertion stereochemistry of deuterated azametallacyclobutane **23**. One pos-

***Scheme 6***



***Scheme 8***



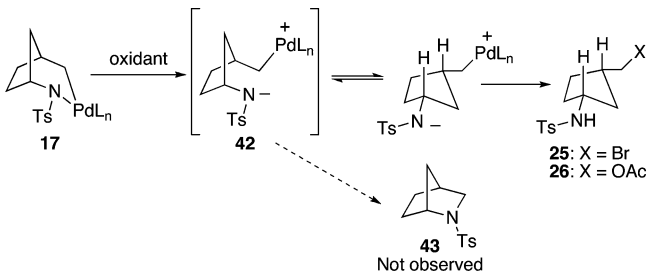

sible mechanistic pathway would involve coordination of copper(I) to the olefin to provide **35**,[40] which may be activated for nucleophilic attack by the palladium-bound alkyl (Scheme 7). Transmetalation of the resulting copper(I) alkyl species (**36**) to palladium would afford **37**,[41] the product of formal anti carbopalladation. This mechanistic pathway can be ruled out, as **37** is not generated. Instead, product **24**, which formally derives from syn carbopalladation, is formed.

A more plausible pathway that is consistent with the formation of a product resulting from syn carbopalladation is shown in Scheme 8. Initial transmetalation of the palladium tosylamide ligand of **23** to copper(I) could afford an alkylpalladium(II) iodide intermediate (**38**).[42] This species could then undergo syn carbopalladation via conformation **38**$^{ax}$, which is unstrained and does not possess the anti-Bredt characteristics that are exhibited in transition state **33** described above (Scheme 6). The carbopalladation would provide **39**, which could undergo transmetalation of the copper(I) tosylamide to yield the observed product **24**.[42,43]

Curiously, the most plausible conformation through which intermediate **38** would be transformed to the observed product bears the −N(Ts)Cu substituent in a pseudoaxial position (**38**$^{ax}$). Cyclization via conformer **38**$^{eq}$, in which the −N(Ts)Cu group is pseudoequatorial, would afford **40**. This complex contains a trans relationship between the Pd group and the copper−sulfonamide moiety and therefore could not undergo cyclization to provide **24**. Instead, **40** would be expected to undergo competing $\beta$-hydride elimination to generate methylenecyclopentane product **41**. One possible explanation for this observation is that the pseudoaxial orientation of the −N(Ts)Cu group could be favored by bridging of the iodide ligand between the Cu and Pd centers in **38**$^{ax}$. Alternatively, **38**$^{ax}$ may simply be the more reactive conformation for the alkene insertion process.

**Oxidatively Induced Reductive Elimination of 17.** Treatment of bicyclic palladium complex **17** with $CuBr_2$ or $PhI(OAc)_2$ effected C−X bond-forming reductive elimination to provide bromide **25** or acetate **26**, respectively. Interestingly, carbon−nitrogen bond-forming reductive elimination to afford azanorbornane **43** was not observed with these or other oxidants. This may be due to a high transition state energy for the formation of the strained product via an inner-sphere reductive elimination.[11i] Alternatively if the reductive elimination proceeds through an outer-sphere mechanism,[16a−d,18] conversion of **17** to **43** would involve dissociation of the tosylamide ligand from palladium to afford aminocyclopentane intermediate **42** followed by $S_N2$-type C−N bond-forming reductive elimination (Scheme 9).[44] This pathway would also require a strained transition state in which both groups occupy pseudoaxial orientations. In contrast, reductive elimination to generate a C−Br or C−OAc bond through either an inner-sphere or outer-sphere process would not require a similarly strained transition state and should be more facile than C−N bond formation in this system.

***Scheme 9***




**Summary of Pd-Mediated Conversion of 7 to 25.** Overall, the transformations described in Table 1, entry 6, and eqs 3 and 4 result in a three-step conversion of aziridine **7** to bromide

(40) For a review on the chemistry of Cu(I) alkene complexes see: Wang, X.-S.; Zhao, H.; Li, Y.-H.; Xiong, R.-G.; You, X.-Z. *Top. Catal.* **2005**, *35*, 43−61.

(41) The stereochemical outcome of transmetalation reactions between well-defined alkylcopper(I) reagents and palladium has not been established. However, related Cu-mediated transmetalation reactions between alkyltin reagents have been shown to proceed with retention of configuration and are believed to proceed through intermediate alkylcopper species. Direct transmetalation of alkyl Sn, B, and Si reagents to Pd are also known to proceed with retention of configuration. See: (a) Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458−460. (b) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461−470. (c) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793−7794. (d) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1−5. (e) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973−5982.

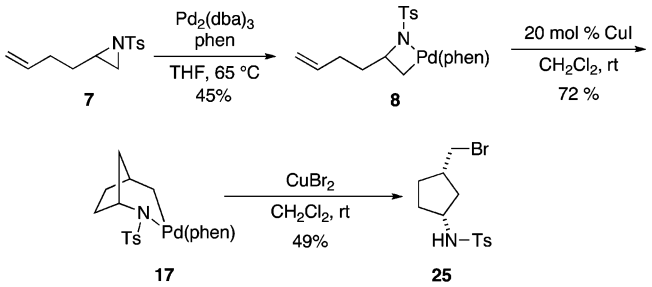
(42) For examples of reversible transmetalation reactions of palladium amido complexes see: (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708−4709. (b) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598−11599.

(43) An alternative mechanism could involve Cu-mediated dechelation of one nitrogen atom in the phenanthroline ligand to afford a coordinatively unsaturated complex, which would be expected to be more reactive towards alkene insertion. Although we cannot unambiguously rule out this possibility, the intermediate azametallacyclobutane−alkene complex appears to be strained, and the transition state for insertion via this pathway would possess anti-Bredt characteristics similar to those described above in Scheme 6.

(44) To the best of our knowledge, no related examples of $S_N2$-type ring closure to form azanorbornane structures have been reported. However, the intramolecular O-alkylation of *cis*-3-hydroxymethylcyclopentanol to afford 2-oxanorbornane has been described. See: Kirmse, W.; Mrotzeck, U. *Chem. Ber.* **1988**, *121*, 485−492.

**25** (Scheme 10) that would be difficult to achieve using other methods. These three reactions effect difunctionalization of the alkene with 1,2-addition of a Br atom and the C1 atom, which can be viewed as a formal reversal of polarity of the electrophilic aziridine carbon. Although this process is not yet catalytic, the individual transformations all occur under mild and essentially neutral reaction conditions. The overall process should be of significant interest if catalytic conditions can be developed, as molecules that are structurally related to **25** have been employed as intermediates in the construction of natural products and other biologically active molecules.[45]

***Scheme 10***




## Conclusions

In conclusion, we have described the first syntheses of azapalladacyclobutane complexes **1**, which are effected via oxidative addition of *N*-sulfonylaziridines to mixtures of $Pd_2(dba)_3$/phen. These metallacycles undergo intramolecular syn carbopalladation in the presence of copper(I) iodide to afford azapalladabicyclo[3.2.1]octanes in the first examples of alkene insertions into azametallacyclobutanes. The unusual bridging bicyclic complexes generated in the insertion reactions undergo oxidative cleavage of the palladium−carbon bond to afford substituted cyclopentylamine derivatives. These transformations have the potential for application to the development of new metal-catalyzed ring expansion reactions of aziridines and represent an unusual three-step *umpolung* process in which the polarization of the aziridine C1 atom is formally reversed. Efforts to render these reactions catalytic and to expand the scope of the oxidative addition and insertion chemistry are currently underway.

## Experimental Section

**General Procedure for the Synthesis of Azapalladacyclobutanes.**[46] A flame-dried Schlenk flask equipped with a magnetic stir bar was charged with $Pd_2(dba)_3$ (0.5 mmol, 1.0 mmol Pd) and 1,10-phenanthroline (1.0 mmol). The flask was purged with nitrogen, THF (50 mL) was added, and the mixture was stirred at room temperature for 1 min. A solution of the aziridine (1.0−1.5 mmol) in THF (50 mL) was added, and the reaction mixture was heated to 65 °C with stirring for 5 h. The mixture was then cooled to room temperature and transferred to a clean, flame-dried Schlenk flask via cannula filtration under nitrogen. The solution was concentrated under reduced pressure to a volume of 5−10 mL, and ether (50 mL) was added to afford a yellow precipitate. The solid material was collected by vacuum filtration, washed with ether (4 × 50 mL) and hexane (2 × 50 mL), and dried in vacuo.

**(Phen)Pd{NTsCH(CH$_2$CH$_2$CHCH$_2$)CH$_2$} (8).** Reaction of 377 mg (1.5 mmol) of **7** with 458 mg (0.5 mmol) of $Pd_2(dba)_3$ and 180 mg (1.0 mmol) of 1,10-phenanthroline following the general procedure afforded 262 mg (49%) of the title compound as a yellow solid, mp 185 °C (decomp). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.06 (dd, $J$ = 1.5, 5.0 Hz, 1 H), 8.54 (dd, $J$ = 1.5, 5.0 Hz, 1 H), 8.49 (dd, $J$ = 1.5, 8.5 Hz, 1 H), 8.40 (dd, $J$ = 1.5, 8.5 Hz, 1 H), 8.09 (d, $J$ = 8.5 Hz, 2 H), 7.92 (s, 2 H), 7.84 (dd, $J$ = 5.0, 8.0 Hz, 1 H), 7.68 (dd, $J$ = 5.0, 8.5 Hz, 1 H), 7.16 (d, $J$ = 8.0 Hz, 2 H), 5.79−5.70 (m, 1 H), 4.97−4.84 (m, 2 H), 4.51−4.45 (m, 1 H), 2.34 (s, 3 H), 2.08−1.93 (m, 2 H), 1.61−1.48 (m, 2 H), 1.12 (dd, $J$ = 5.0, 8.0 Hz, 1 H), 0.57 (app t, $J$ = 5.0 Hz, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 153.4, 149.4, 146.8, 144.7, 141.7, 140.6, 139.5, 137.5, 137.1, 129.9, 129.3, 128.9, 128.0, 127.8, 126.5, 126.1, 124.8, 113.9, 68.7, 38.5, 29.1, 21.6, −6.0; IR (film) 1127, 1084 cm$^{-1}$; MS (ESI) $m/z$ 560.0613 (560.0600 calcd for $C_{25}H_{25}N_3O_2PdS$, M + Na$^+$).

**(Phen)Pd{NTsCH(CH$_2$CH$_2$)CH$_2$CHCH$_2$} (17).** A flame-dried Schlenk flask equipped with a magnetic stir bar was charged with CuI (15 mg, 0.078 mmol). The flask was purged with nitrogen, and then a solution of **8** (210 mg, 0.39 mmol) in 39 mL of $CH_2Cl_2$ was added. The reaction mixture was stirred at room temperature for 20 h and then transferred to a clean, flame-dried Schlenk flask via cannula filtration under nitrogen. The solution was concentrated under reduced pressure to a volume of 3 mL, and ether (50 mL) was added to afford an orange precipitate. The solid material was collected by vacuum filtration, washed with ether (4 × 50 mL) and hexane (2 × 50 mL), and dried in vacuo to afford the title compound (171 mg, 81%) as an orange solid, mp 185 °C (decomp). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.64 (d, $J$ = 4.0 Hz, 1 H), 8.84 (d, $J$ = 4.5 Hz, 1 H), 8.48 (d, $J$ = 8.0 Hz, 1 H), 8.36 (d, $J$ = 7.5 Hz, 1 H), 8.12 (d, $J$ = 8.0 Hz, 2 H), 7.90−7.82 (m, 3 H), 7.76 (dd, $J$ = 5.0, 8.0 Hz, 1 H), 7.22 (d, $J$ = 7.5 Hz, 2 H), 3.87−3.83 (m, 1 H), 2.39 (s, 3 H), 2.05−1.97 (m, 1 H), 1.92−1.84 (m, 1 H), 1.84−1.81 (m, 1 H), 1.81−1.74 (m, 1 H), 1.68−1.63 (m, 1 H), 1.63−1.58 (m, 1 H), 1.45−1.40 (m, 1 H), 1.22−1.15 (m, 1 H), 1.09−1.04 (m, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 151.5, 148.0, 147.9, 144.5, 143.5, 140.0, 137.8, 136.7, 130.0, 129.2, 128.8, 128.3, 127.5, 126.3, 125.4, 124.5, 56.6, 39.6, 38.3, 34.4, 30.6, 27.8, 21.6; IR (film) 1263, 1132, 1092 cm$^{-1}$; MS (ESI) $m/z$ 560.0604 (560.0600 calcd for $C_{25}H_{25}N_3O_2PdS$, M + Na$^+$).

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**Supporting Information Available:** Experimental procedures, characterization data for all new compounds, descriptions of deuterium-labeling experiments, descriptions of structural and stereochemical assignments, and selected one- and two-dimensional NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(46) The yields reported in the Experimental Section and the Supporting Information describe the result of a single experiment, whereas the yields reported in Tables 1 and 2, Schemes 2 and 3, and eqs 3 and 4 are average yields of two or more experiments. Thus, the yields reported in the Experimental Section and Supporting Information may differ from those shown in Tables 1 and 2, Schemes 2 and 3, and eqs 3 and 4.