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Palladium-Catalyzed Synthesis of Cyclopentane-Fused Benzocyclobutenes via Tandem Directed Carbopalladation/ C–H Bond Functionalization

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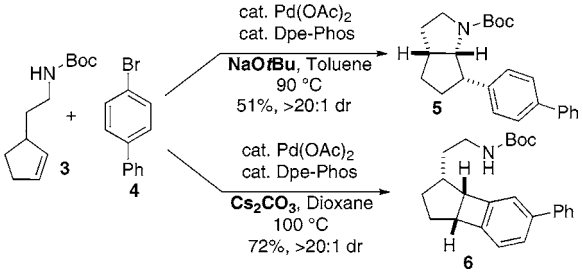
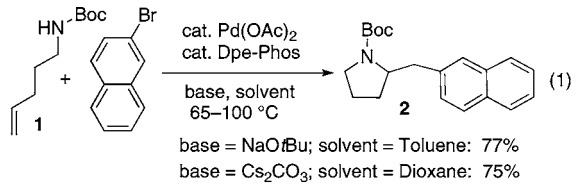
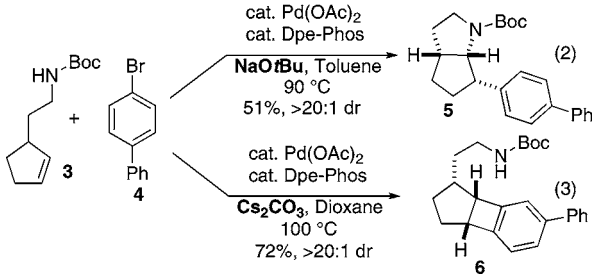
ABSTRACT



A new Pd-catalyzed reaction for the stereoselective synthesis of cyclopentane-fused benzocyclobutenes is described. These transformations likely proceed via carbamate-directed carbopalladation followed by intramolecular C–H activation of an alkylpalladium intermediate. The mechanistic relationship between these transformations and Pd-catalyzed reactions of γ-(*n*-Boc-amino)alkenes with aryl bromides that afford pyrrolidines is discussed. Differences in reactivity between Pd-amino and Pd-amido complexes appear to play a key role in the outcome of these transformations.

During the course of studies on Pd-catalyzed carboamination reactions of N-protected γ-aminoalkenes[1] we observed that the use of the weak base Cs_2CO_3 in transformations of terminal alkene substrates (e.g., **1**) provided 2-benzylpyrrolidine derivatives (e.g., **2**) in yields that were comparable to those obtained with the stronger base NaO*t*Bu (eq 1).[2] However, when the Cs_2CO_3 conditions were employed with cyclopentene-derived substrate **3**, a surprising result was obtained. As shown below, the Pd-catalyzed reaction of **3** with 4-bromobiphenyl (**4**) in the presence of Cs_2CO_3 did not provide the expected product **5**, but instead generated benzocyclobutene derivative **6** in 72% yield and >20:1 dr (eq 3). This result is in marked contrast with the reaction of **3** with **4** in the presence of NaO*t*Bu,[1b] which affords the expected heterocycle **5** in 51% yield (eq 2).[3]





(1) (a) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605. (b) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447. (c) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644. (d) Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353. (e) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571 and references cited therein.

(2) Bertrand, M. B.; Leathen, M. L.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 457.

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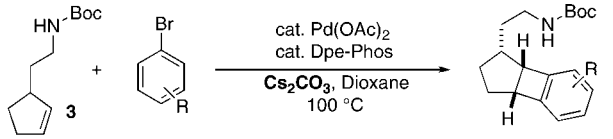
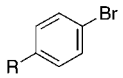
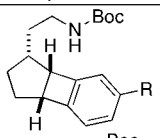
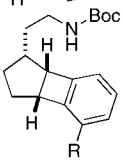
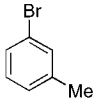
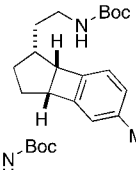
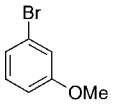
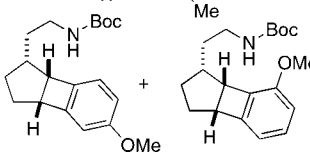
The generation of benzocyclobutene **6** is both synthetically and mechanistically interesting.[4] Benzocyclobutenes are widely employed as precursors to *o*-quinodimethides, which are known to undergo facile [4+2] cycloaddition reactions,[5] and can also be employed in polymerizations.[6] Moreover, the surprising effect of base on the reactivity of **3** raises questions about the mechanistic relationship between the reactions shown in eqs 1−3. In this Letter we describe our preliminary studies on the preparation of benzocyclobutenes via coupling of **3** with aryl bromides, and present a mechanistic hypothesis that accounts for the observed effect of base on these transformations.

To explore the scope of the Pd-catalyzed benzocyclobutene forming process, we examined reactions of **3** with various para-, meta- and ortho-substituted aryl bromides. As shown in Table 1, reactions of para-substituted starting materials

Table 1. Synthesis of Benzocyclobutenes from **3**[a]



entry	ArBr	product	yield (%)[b,c]
1			R = CH_2OAc: 74
2			R = Ph: 72
3			R = Cl: 70
4			R = OMe: 58
5			R = Me: 85
6			R = Ph: 80
7			68
8			66 (2:1)

[a] Conditions: 1.0 equiv of **3**, 1.2. equiv of ArBr, 2.3 equiv of Cs_2CO_3, 4 mol % of $Pd(OAc)_2$, 8 mol % of Dpe-Phos, dioxane (0.25 M), 100 °C. [b] Yields refer to average isolated yields obtained in two or more experiments. [c] All products were obtained with >20:1 dr and >20:1 regioselectivity unless otherwise noted.

afforded products substituted exclusively at the 5-position of the aromatic ring (entries 1−4). Similarly high regioselectivity was obtained in reactions of ortho-substituted aryl bromides, which afforded products bearing substituents at the 3-position (entries 5 and 6). The regioselectivities observed in reactions of meta-substituted aryl bromides were dependent on the nature of the substituent. Although the reaction of **3** with *m*-bromotoluene proceeded with good regioselectivity (entry 7), the coupling of **3** with *m*-bromoanisole afforded a 2:1 mixture of regioisomers (entry 8).

The major side products formed in reactions between **3** and either electron-rich or electron-neutral aryl bromides were arylated cyclopentanes (**7**), although in many reactions trace amounts of bicyclic products **8**−**10** were detected by ^{1}H NMR analysis of the crude reaction mixtures (Figure 1).[7]

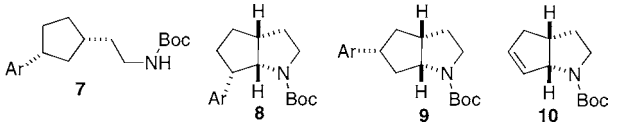
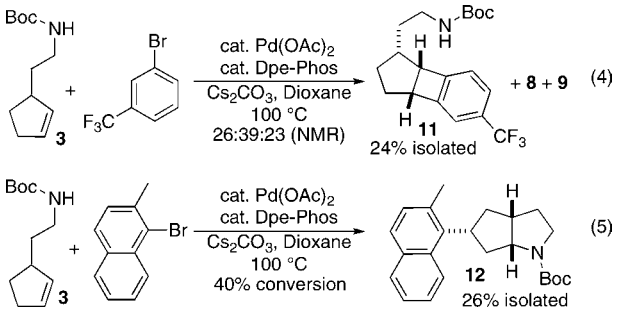


Figure 1. Side products.

Although the benzocyclobutene-forming reactions proceeded smoothly with many aryl bromides, the Pd-catalyzed coupling of **3** with the electron-poor substrate 3-bromobenzotrifluoride afforded a 26:39:23 mixture of **11**:**8**:**9** (eq 4);[8] upon purification **11** was obtained in 24% yield. In addition, the Pd-catalyzed reaction of **3** with 1-bromo-2-methylnaphthalene proceeded slowly and in low conversion (ca. 40%) to afford 5-aryl azabicyclo[3.3.0]octane **12** in 26% isolated yield (eq 5).[9]



The dependence of base on the outcome of Pd-catalyzed reactions of **3** with aryl bromides (eqs 2 and 3) likely results from differences in reactivity of palladium *amino* complexes vs palladium *amido* complexes.[10] As shown in Scheme 1, oxidative addition of the aryl bromide to Pd(0) generates **13**, which can bind the carbamate to provide **14**. In the presence of a base, *amino* complex **14** can potentially be

(3) Dpe-Phos = bis(2-diphenylphosphinophenyl) ether.

(4) For Pd-catalyzed reactions of aryl bromides with norbornene and related bicyclo[2.2.*n*]alkenes that afford benzocyclobutene products, see: (a) Catellani, M.; Chiusoli, G. P.; Ricotti, S. *J. Organomet. Chem.* **1985**, *296*, C11. (b) Catellani, M.; Chiusoli, G. P.; Ricotti, S.; Sabini, F. *Gazz. Chim. Ital.* **1985**, *115*, 685. (c) Catellani, M.; Ferioli, L. *Synthesis* **1996**, 769.

(5) (a) Sadana, A. K.; Saini, R. K.; Billups, W. E. *Chem. Rev.* **2003**, *103*, 1539. (b) Mehta, G.; Kotha, S. *Tetrahedron* **2001**, *57*, 625.

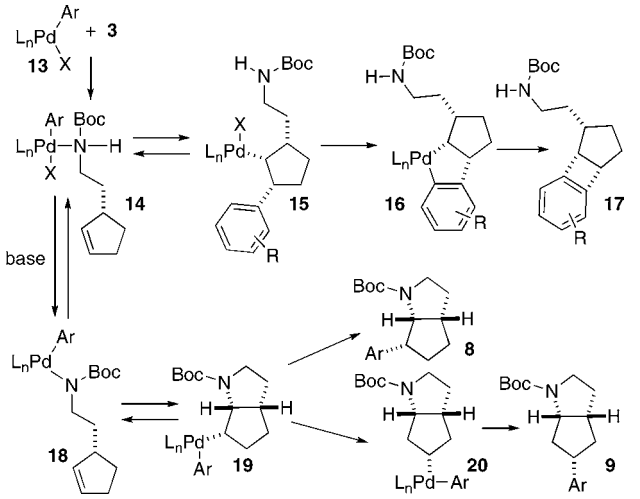
(6) Farona, M. F. *Prog. Polym. Sci.* **1996**, *21*, 505.

(7) These structures were assigned by comparison of NMR spectra to those obtained for isolated samples of **5**, **12**, and a previously described *N*-aryl analogue of **10**. See ref 1c.

(8) The remainder of the mixture consisted of 5% *N*-arylated substrate and 8% of unidentified products.

(9) A similar result was obtained with 2-bromo-*m*-xylene, which afforded a 5-aryl azabicyclo[3.3.0]octane in 30% yield (ca. 40% conversion). See the Supporting Information for complete details.

Scheme 1



converted to *amido* complex **18**. However, with the weak base Cs_2CO_3 this process should be relatively slow due to the low solubility of Cs_2CO_3,[10] and the equilibrium between **14** and **18** may favor **14**. In contrast, when the relatively strong, soluble base NaO*t*Bu is employed, the conversion of **14** to **18** is relatively fast, and the equilibrium favors amido complex **18**.[10,11]

The benzocyclobutene products formed when Cs_2CO_3 is used as base are likely generated via directed carbopalladation[12,13] of *amino* complex **14** to provide the sterically hindered alkylpalladium intermediate **15**, which lacks β-hydrogen atoms *syn* to the metal. Intramolecular aryl C−H bond activation[4,14] of **15** provides **16** and an equivalent of HBr, which is neutralized by Cs_2CO_3. Complex **16** is then converted to benzocyclobutene **17** via C−C bond-forming reductive elimination.[4,15] The arylated cyclopentane side product **7** may result from competing protonation of the Pd−C bond(s) of **15** or **16**. The conversion of the electron-poor *m*-bromobenzotrifluoride to a mixture of **11**, **8**, and **9** is likely due to enhancement of the N−H proton acidity of **14** when the complex bears an electron-withdrawing aryl substituent, which would shift the **14**/**18** equilibrium toward **18**.

Under conditions that facilitate rapid and/or thermodynamically favorable formation of *amido* complex **18**, the reactions likely proceed via *syn*-amidopalladation as described previously to generate **19**,[1] which is converted to **8** via C−C bond-forming reductive elimination. Alternatively, **19** can also be transformed to **9** or **10** via β-hydride elimination/reinsertion processes.[1a,c]

The differences in reactivity observed between substrates bearing terminal alkenes (e.g., **1**) and cycloalkene substrate **3** may be due either to the influence of alkene size on the position of the **18**/**19** equilibrium, the influence of substrate sterics on the rate of C−C bond-forming reductive elimination from **19**, or the influence of alkene substitution on the relative rates of alkene insertion into the Pd−C bond of **14** vs the Pd−N bond of **18**. In addition, the fact that Pd-catalyzed reactions of **3** with aryl halides lacking *o*-hydrogen atoms are converted to azabicyclooctanes (e.g., **12**) in the presence of Cs_2CO_3 suggests that the carbopalladation of **14** is either reversible[16] or very slow with bulky aryl groups. Our current data do not allow us to differentiate between these possibilities.

In conclusion, we have developed a new transformation for the conversion of **3** to cyclopentane-fused benzocyclobutenes via an unprecedented sequence of heteroatom-directed carbopalladation followed by intramolecular aryl C−H bond activation. These are the first examples of reactions that use directed carbopalladation for the generation and functionalization of alkylpalladium intermediates that lack *syn*-β-hydrogen atoms. Importantly, the results described above also illustrate that differences in reactivity between Pd-*amino* and Pd-*amido* complexes can be exploited to allow the construction of strikingly different products from common starting materials. Further studies on the scope of this method and applications of these concepts are currently underway.

Acknowledgment. The authors thank the NIH-NIGMS (GM-071650) for financial support of this work. Additional support was provided by the Camille and Henry Dreyfus Foundation, Research Corporation, Eli Lilly, Amgen, and 3M.

Supporting Information Available: Experimental procedures and characterization data for new compounds and X-ray crystal structure of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) *Amino* complex refers to coordination of the neutral carbamate, whereas *amido* complex refers to coordination of the deprotonated, anionic carbamate. For discussion of kinetic and thermodynamic effects in amido complex formation, see: (a) Meyers, C.; Maes, B. U. W.; Loones, K. T. J.; Bal, G.; Lemiere, G. L. F.; Dommisse, R. A. *J. Org. Chem.* **2004**, *69*, 6010. (b) Driver, M. S.; Hartwig, J. F. *Organometallics* **1997**, *16*, 5706.

(11) When NaO*t*Bu is employed as base the amido complex could also be generated via reaction of **13** with deprotonated carbamate, or through reaction of the carbamate with a LnPd(Ar)(O*t*Bu) complex. See: Shekhar, S.; Hartwig, J. F *Organometallics* **2007**, *26*, 340.

(12) For early examples, see: (a) Kasahara, A.; Izumi, T.; Takeda, T.; Imamura, H. *B. Chem. Soc. Jpn.* **1974**, *47*, 183. (b) Andersson, C.-M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757.

(13) For a recent review see: Oestreich, M. *Eur. J. Org. Chem.* **2005**, 783.

(14) For recent reviews, see: (a) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (b) Catellani, M. *Synlett* **2003**, 298.

(15) For tandem intermolecular carbopalladation/C−H functionalization processes involving alkenylpalladium intermediates, see: (a) Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927. (b) Furuta, T.; Asakawa, T.; Iinuma, M.; Fujii, S.; Tanaka, K.; Kan, T. *Chem. Commun.* **2006**, 3648.

(16) (a) Campora, J.; Gutierrez-Puebla, E.; Lopez, J. A.; Monge, A.; Palma, P.; del Rio, D.; Carmona, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3641. (b) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 119.