Palladium Amido Complexes

DOI: 10.1002/anie.200904032

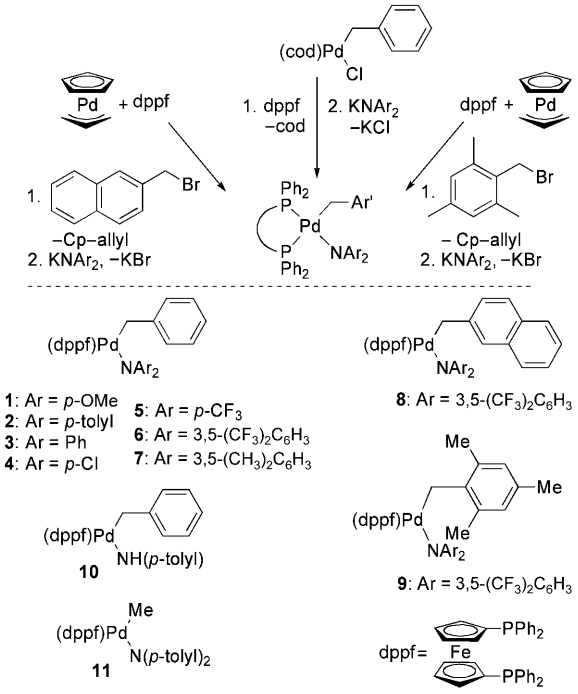
C(sp^3)–N Bond-Forming Reductive Elimination of Amines: Reactions of Bisphosphine-Ligated Benzylpalladium(II) Diarylamido Complexes**

*Seth L. Marquard, Devon C. Rosenfeld, and John F. Hartwig**

Reductive elimination is a common organometallic transformation that is the key product-forming step in many catalytic cycles.[1] Although many examples of reductive elimination from aryl palladium amido complexes to form C(sp^2)–N bonds have been reported as part of catalytic processes and as stoichiometric reactions,[2,3] reductive elimination to form a bond between an amide ligand and an sp^3-hybridized carbon atom is less common. Reductive elimination from methylplatinum(IV) sulfonamido complexes by dissociation of the sulfonamide has been reported,[4] as has reductive elimination from alkyl nickel amido complexes after the addition of an oxidant.[5,6] Reactions of free amines with allyl- and benzylpalladium complexes are also known.[7–9] However, despite several attempts,[10,11] reductive elimination to form an C(sp^3)–N bond of any type through the simple thermal reaction of an isolated organometallic amido complex has not been reported.

Herein, we report a purely thermal reductive elimination to form a C(sp^3)–N bond in an amine from a benzylpalladium amido complex. An assessment of the stereochemical course of this process showed that it occurs by a stepwise pathway that is distinct from the accepted concerted pathway for the reductive elimination of aromatic amines from aryl palladium(II) species, and an assessment of the effect of the electronic properties of the amido group on the reaction rate showed that this effect is distinct from that observed for reductive elimination to form C–O bonds from methylplatinum(IV) carboxylate and phenoxide complexes.

We prepared a series of benzylpalladium amido complexes to investigate their ability to undergo reductive elimination to form C(sp^3)–N bonds without competing β-hydrogen elimination. We chose complexes containing chelating ligands to enforce a *cis* configuration of the benzyl and the amido ligands for reductive elimination; complexes containing a 1,1′-bis(diphenylphosphanyl)ferrocene (dppf) ligand displayed the appropriate balance of stability, reactivity, and synthetic accessibility. Dppf-ligated benzylpalladium amido complexes **1**–**7** were synthesized by treatment of the known complex [(cod)Pd(Bn)Cl][9] (Bn = benzyl) with dppf followed by the appropriate potassium diarylamide in THF (Scheme 1). Complexes **8** and **9**, which contain naphthylmethyl and mesitylmethyl groups, respectively, were synthesized by the treatment of [CpPd(η^3-allyl)][12] with dppf followed by naphthylmethyl or mesitylmethyl bromide. The resulting bromide complexes were then converted into the diarylamido complexes by treatment with the appropriate potassium diarylamide. The benzylpalladium arylamido complex **10** and methylpalladium diarylamido complex **11** were synthesized by analogous methods involving the treatment of [(cod)Pd(Bn)Cl] with dppf followed by the potassium anilide, and the treatment of [(cod)Pd(Me)Cl][13] with dppf followed by the potassium diarylamide. These compounds were characterized by conventional one- and two-dimensional NMR spectroscopic methods and elemental analysis.



Scheme 1. Synthesis of palladium amido complexes. cod = 1,5-cyclooctadiene.

To assess the ability of complexes **1**–**11** to undergo reductive elimination, we heated solutions of these complexes

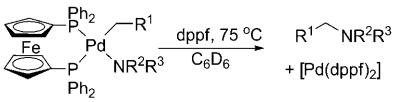
[*] S. L. Marquard, Dr. D. C. Rosenfeld, Prof. Dr. J. F. Hartwig
Department of Chemistry
University of Illinois Urbana-Champaign
Urbana, IL 61801 (USA)
Fax: (+1) 217-244-8024
E-mail: jhartwig@illinois.edu

[**] This research was supported by the NSF as part of the Center for Enabling New Technologies through Catalysis (CENTC), CHE-0650456. We thank Luc Boisvert and Karen Goldberg at the University of Washington for helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200904032.

in benzene at 75 °C. The reactions were conducted with added dppf to trap the Pd^0 product. The benzyl complexes **1**–**7** and naphthylmethyl complex **8** underwent reductive elimination in high yields (Table 1). The mesitylmethyl complex **9** also

Table 1: C(sp^3)–N bond-forming reductive elimination.



Complex	R^1	R^2,R^3	Yield [%][a]	$t_{1/2}$ [min][b]
1	Ph	*p*-OMe	62[c]	33[c]
2	Ph	*p*-tolyl	83	73[d]
3	Ph	Ph	88	72
4	Ph	*p*-Cl	87	43
5	Ph	*p*-CF_3	93[e]	79
6	Ph	3,5-$(CF_3)_2C_6H_3$	83	>1400[f]
7	Ph	3,5-$(CH_3)_2C_6H_3$	63	97
8	naphthyl	3,5-$(CF_3)_2C_6H_3$	83	<10[f]
9	mesityl	3,5-$(CF_3)_2C_6H_3$	25[g]	12[f,h]
10	Ph	H, *p*-tolyl	0	–
11	H	*p*-tolyl	0	–

[a] The yield was determined by ^{1}H NMR spectroscopy relative to trimethoxybenzene as an internal standard. [b] Reactions to determine rate constants and half-lives were conducted in [D_6]benzene at 55 °C, unless otherwise noted. The $t_{1/2}$ values were determined from k_{obs} values over three half-lives, unless otherwise noted. [c] The reaction was conducted at 55 °C in THF. [d] When conducted in THF at 55 °C, this reaction occurred with a half-life of 65 min. [e] The reaction was conducted at 55 °C. [f] The $t_{1/2}$ value was estimated by monitoring the reactions, by ^{1}H NMR spectroscopy with an internal standard, to approximately 50% conversion. [g] The (2,3,5-trimethylbenzyl)diarylamine was also formed in 26% yield. [h] The reaction was conducted at 30 °C.

underwent reductive elimination, in this case to form a mixture of the (mesitylmethyl)diarylamine (25%), the (2,3,5-trimethylbenzyl)diarylamine (26%), and the free diarylamine by an unknown protonolysis (46%). We presume the (2,3,5-trimethylbenzyl)diarylamine product forms by rearrangement of the hindered mesitylmethyl complex to the less hindered 2,3,5-trimethylbenzyl species during the reductive-elimination process.[14]

In contrast, the less hindered anilide complex **10** and the methyl complex **11** did not form products of reductive elimination at 75 °C. Free H_2N(*p*-tolyl) and bibenzyl formed upon the heating of anilide complex **10**, as determined by GC/MS, and HN(*p*-tolyl)$_2$ formed when the diarylamido complex **11** was heated. The proton source in these reactions is unknown.

Several experiments provided information on the effect of the electronic properties of the amide ligand on the rate of this reductive elimination. The half-lives for reactions of the various amido complexes are included in Table 1. Reductive elimination from complex **5**, which contains an electron-withdrawing *p*-CF_3 group, was slower than that from the di-*p*-tolylamido complex **2**, and reductive elimination from complex **1**, which contains an electron-donating *p*-OMe group, was faster than that from complex **2**, although the rate differences were not large. Complex **2** and the diphenylamido complex **3** reacted at nearly identical rates. The *p*-chloroamido complex **4** reacted somewhat faster than the ditolylamido complex **2**, which suggests that π donation from the aryl groups may be important. From this assessment, the rate of reductive elimination is moderately influenced by the electronic properties of the amido group, and the complexes containing more electron rich amido groups react faster.

The substitution pattern of the amido group had a substantial influence on the rate of reductive elimination. Amido complexes containing substituents at the 3- and 5-positions of the amido aryl groups reacted more slowly than those containing a substituent at the 4-position: the di-*m*-xylylamide complex **7** underwent reductive elimination more slowly than di-*p*-tolylamido complex **2**, and complex **6**, which contains trifluoromethyl substituents in the 3- and 5-positions of the aryl groups on the amido ligand, underwent reductive elimination by far the most slowly. We do not have a firm explanation for the difference in the reaction rates of the complexes containing 3,5-disubstituted and 4-substituted diarylamido ligands.

The observation that complexes containing more electron rich amido groups underwent reductive elimination more rapidly than those containing less electron rich amido groups with the same substitution pattern contrasts with the relative rates found by Goldberg and co-workers[15] for the reductive elimination of aryl methyl ethers from methylplatinum(IV) phenoxide complexes. Given these electronic effects on the rate of the reaction, it is surprising that the anilido complex **10** does not undergo reductive elimination. Apparently, the steric properties of the amido ligand have a large impact on the rate of reductive elimination.

The effect of the benzyl group on the rate of reductive elimination was revealed by comparing the reaction of complex **6** to those of the naphthylmethyl complex **8** and the more hindered mesitylmethyl complex **9**. The naphthylmethyl complex **8** and the mesitylmethyl complex **9** reacted faster than the analogous benzyl complex **6**. The rate constant for reductive elimination from the naphthylmethyl complex **8** was at least 140 times larger than the rate constant for the overall C–N bond-forming process from **6**, and the rate constant for reductive elimination from the mesitylmethyl complex **9** (at 30 °C) was 40–50 times larger than that for reductive elimination from **6** (at 55 °C).

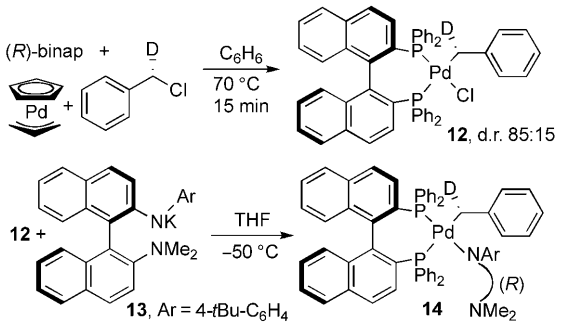
The reductive-elimination reactions reported herein could occur by a concerted, an ionic, or a radical pathway. The configuration at the benzylic carbon atom can be used to distinguish these mechanisms. A concerted reductive elimination would lead to retention of configuration, sequential dissociation of the amide and backside attack on the benzyl group would cause inversion of configuration, and reaction via a benzyl radical would cause racemization at this carbon atom.

Previously, the stereochemical course of reactions of metal–benzyl complexes was determined by measurements of optical rotation or the use of a chiral shift reagent to assess the configuration of organic products.[16,17] Stille and co-workers determined that the oxidative addition of benzyl halides to [$Pd(PPh_3)_4$] occurred with inversion of configuration by

cleaving the benzyl group from the addition product with CO and methanol and analyzing the alcohol formed by reduction of the resulting ester. The stereochemical course of reactions of alkyl complexes has also been determined with deuterated, diastereomeric *tert*-butylethyl derivatives, but the use of such complexes is limited by their propensity to undergo β-hydrogen elimination when an open coordination site is present. Thus, we devised a new, more direct, strategy to determine the stereochemical course of reactions of metal–benzyl complexes that does not rely on optical rotation or require an interaction of the product with a chiral shift reagent.

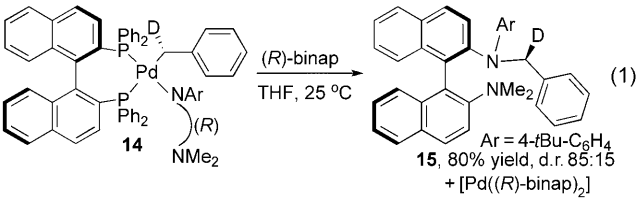
Our strategy involves the use of a chiral, nonracemic phosphine, a chiral, nonracemic amido group, and an enantiomerically enriched monodeuterobenzyl group. The chiral ligand enables determination of the relative ratio of benzylpalladium halide precursors with an *R* or *S* configuration at the benzylic position, and the chiral amido group enables determination of the configuration of the benzylic carbon atom in a diastereomeric amine product. We tested several ligands and chiral auxiliaries and found that the ^{1}H NMR spectra of the starting complexes and products containing 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (binap) as the dative ligand and a binaphthyl group on the amide ligand displayed well-resolved benzylic signals.

The monodeuterated benzylpalladium chloride complex **12** was synthesized in an 85:15 diastereomeric ratio in favor of the R_a,R_c isomer from [CpPd(η^3-allyl)], (*R*)-binap, and (*S*)-monodeuteriobenzyl chloride (Scheme 2).[18] The configuration at the benzylic carbon atom was deduced by comparing the ^{1}H NMR spectrum of complex **12** generated by this route to that of the complex generated from the known product of oxidative addition of monodeuteriobenzyl chloride to [Pd(PPh$_3$)$_4$].[17,18] Complex **12** was converted into the corresponding R_a,R_a,R_C benzylpalladium binaphthylamido complex **14** by the addition of the potassium R_a binaphthylamide **13** at −50 °C in [D$_8$]THF. Complex **14** was unstable at room temperature (see below) and was therefore characterized at −50 °C by one- and two-dimensional NMR spectroscopic methods. The characteristic benzylic peaks of complex **14** were identified by HMQC, COSY, and selective ^{1}H{^{31}P} NMR spectroscopy.



Scheme 2. Synthesis of the complexes used for stereochemical determination.

Complex **14** underwent reductive elimination of the *N*-benzylbinaphthylamine **15** in 80% yield in 60 minutes at room temperature, as determined by ^{1}H NMR spectroscopy with an internal standard [Eq. (1)]. ^{1}H NMR spectroscopy indicated that the same 85:15 ratio of diastereomers was formed as was present in the intermediate **12**. Comparison of the ^{1}H NMR spectrum of the amine product **15** to that of the same amine prepared independently indicated that the reductive elimination occurred with inversion of configuration to form predominately (R_a,S_c)-**15** (see the Supporting Information). We envision that this configuration results from dissociation of the diarylamide, followed by nucleophilic attack on the benzylic carbon atom. Reactions that occur by the dissociation of amide ligands to form ionic intermediates during organometallic processes are unusual.[5]



(1)

This mechanistic proposal was corroborated by additional experiments. First, the reductive elimination from complex **2** in [D$_6$]benzene at 55 °C occurred with a half-life of 73 minutes, whereas the same reaction of **2** in more polar [D$_5$]nitrobenzene occurred with a shorter half-life of 26 minutes at 55 °C. Second, a first-order decay of **2** was observed, and this result is inconsistent with a potential attack of an intact amido complex on the benzyl group. Although proton donors are known to assist the dissociation of anionic ligands,[4,15,19] the reductive elimination from **2** was not affected greatly by the addition of an amine. The rate constant for reductive elimination from **2** was $(11 \pm 1 \times 10^{-4})$ s^{-1} for reactions conducted with an added amine, the concentration of which ranged from (3.0×10^{-3}) to (9.1×10^{-2}) M (see the Supporting Information).

These results show that the factors that control the rate and scope of this reductive elimination are unique. First, the stepwise process contrasts with the concerted reductive elimination from aryl palladium amide complexes. Second, the reaction occurs without initial oxidation to a higher-valent metal. Third, the ionic mechanism for this reductive elimination from palladium(II) occurs with amido ligands that form less stabilized anions than the tosylamido groups that have been observed to undergo reductive elimination from platinum(IV) or nickel(II) (HNPh$_2$, pK_a = 25; PhS(O)$_2$NH$_2$, pK_a = 16 in dimethyl sulfoxide), and the reaction is faster from complexes containing more electron donating diarylamido ligands than from complexes containing less electron donating diarylamido ligands. Fourth, the reaction is not strongly affected by an added amine that could promote dissociation of the amide. Fifth, this reaction begins with an amido ligand bound to palladium, rather than the free amine used in allylic substitution reactions. Reactions that occur by

the dissociation of an amide ligand, let alone the dissociation of an amide ligand in hydrocarbon solvents to form an ionic intermediate, have not been reported previously. Finally, these results suggest that the functionalization of C–H bonds via palladium(II) species to form carbon–heteroatom bonds occurs by dissociation of the anionic ligand rather than by likely direct reductive elimination.

The greater propensity for reductive elimination to occur from benzyl complexes than from methyl complexes could result from a greater electrophilicity of the benzyl group relative to the methyl ligand, an ability of the benzyl group to stabilize the cationic intermediate by an η^3 interaction and promote dissociation of the amide anion, or the greater steric bulk of the benzyl group. Further studies are needed to define the role of the organic ligand in these reactions, but these preliminary results imply that the rate of reductive elimination is affected by more than one of these factors. Faster reductive elimination from the naphthylmethyl complex, which would form a more stable cationic η^3-benzylic intermediate than that derived from the parent benzyl complex, suggests that the intermediacy of η^3-benzyl complexes can explain the difference in reactivity between benzyl complexes **1**–**9** and the methyl complex **11**. However, the fast reaction of the mesitylmethyl complex **9**, which would form a less stable η^3-benzyl structure but possesses a more crowded coordination sphere, implies that steric congestion significantly increases the rate of reductive elimination and also contributes to the difference in reactivity between complexes **1**–**7** and the arylamido complex **10**. Such steric factors are also likely to contribute to the higher yield of reductive elimination from diarylamido complexes **1**–**7** than from arylamido complex **10**, despite the seemingly more favorable electronic properties of the arylamido ligand for this type of reductive elimination.

In summary, we have described the first direct reductive elimination to form an C(sp^3)–N bond in an amine from an organometallic amido complex. This reaction occurs from a low-valent Group 10 metal center without oxidation. A combination of kinetic and stereochemical studies indicate that this reaction occurs by a stepwise pathway that most likely involves dissociation of a diarylamide anion, followed by nucleophilic attack of the amide onto the resulting cationic benzylpalladium complex. This pathway contrasts with the concerted pathway for the coupling of aryl and amido ligands[20] or the coupling of two alkyl ligands,[21] and the electronic effects of the diarylamido ligand contrast with those of the anionic ligand during reductive elimination from platinum(IV). Studies to probe the origins of these differences and to extend these reactions to reductive elimination from purely alkyl complexes are in progress.

Experimental Section

Typical procedure for the synthesis of the bisphosphine benzylpalladium amido complexes: In a 20 mL scintillation vial, [(cod)Pd(Bn)Cl] (107 mg, 0.313 mmol) was dissolved in THF (5 mL). Dppf (174 mg, 0.313 mmol) was dissolved in THF (5 mL) in another vial, and the resulting solution was added to the stirred solution of [(cod)Pd(Bn)Cl] in a nitrogen-filled glove box. After 10 min, $KN(Ar)_2$ (0.345 mmol) dissolved in THF (5 mL) was added to the orange solution, and the resulting mixture was stirred for 10 min. The THF was then evaporated in vacuo, and the residue was dissolved in toluene. The toluene solution was filtered through a plug of Celite, which was then rinsed with toluene until the color had dissipated. The filtrate was reduced in volume to about 3 mL under reduced pressure, layered with pentane, and cooled to −35 °C for 12 h to complete precipitation. The solid was filtered from the solution, washed with pentanes (3 × 10 mL), and then dried in vacuo.

Received: July 21, 2009
Revised: November 10, 2009
Published online: December 18, 2009

Keywords: amido complexes · C–N bond formation · dissociation · palladium · reductive elimination

[1] J. F. Hartwig, *Organotransition Metal Chemistry: From Bonding to Catalysis*, University Science Books, **2009**, chap. 8.
[2] A. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338.
[3] J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534.
[4] A. V. Pawlikowski, A. D. Getty, K. I. Goldberg, *J. Am. Chem. Soc.* **2007**, *129*, 10382.
[5] K. Koo, G. L. Hillhouse, *Organometallics* **1995**, *14*, 4421.
[6] B. L. Lin, C. R. Clough, G. L. Hillhouse, *J. Am. Chem. Soc.* **2002**, *124*, 2890.
[7] U. Nettekoven, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 1166.
[8] A. M. Johns, J. W. Tye, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 16010.
[9] A. M. Johns, M. Utsunomiya, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 1828.
[10] O. Esposito, A. K. de K. Lewis, P. B. Hitchcock, S. Caddick, F. G. N. Cloke, *Chem. Commun.* **2007**, 1157.
[11] O. Esposito, P. M. P. Gois, A. K. de K. Lewis, S. Caddick, F. G. N. Cloke, P. B. Hitchcock, *Organometallics* **2008**, *27*, 6411.
[12] T. Yoshitaka, Y. Toshikatsu, O. Sei, *Inorg. Syn.* **1990**, *28*, 342.
[13] E. V. Salo, Z. Guan, *Organometallics* **2003**, *22*, 5033.
[14] No isomerization of the starting diarylamido complex was observed during the reaction.
[15] B. S. Williams, K. I. Goldberg, *J. Am. Chem. Soc.* **2001**, *123*, 2576.
[16] Y. Becker, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 838.
[17] K. S. Y. Lau, P. K. Wong, J. K. Stille, *J. Am. Chem. Soc.* **1976**, *98*, 5832.
[18] See the Supporting Information for ^{1}H NMR spectra.
[19] N. A. Smythe, K. A. Grice, B. S. Williams, K. I. Goldberg, *Organometallics* **2009**, *28*, 277.
[20] M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 8232.
[21] D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1979**, *101*, 4981.

