C–H Activation

Deutsche Ausgabe: DOI: 10.1002/ange.201502075
Internationale Ausgabe: DOI: 10.1002/anie.201502075

Palladium(0)/PAr_3-Catalyzed Intermolecular Amination of C(sp^3)–H Bonds: Synthesis of β-Amino Acids**

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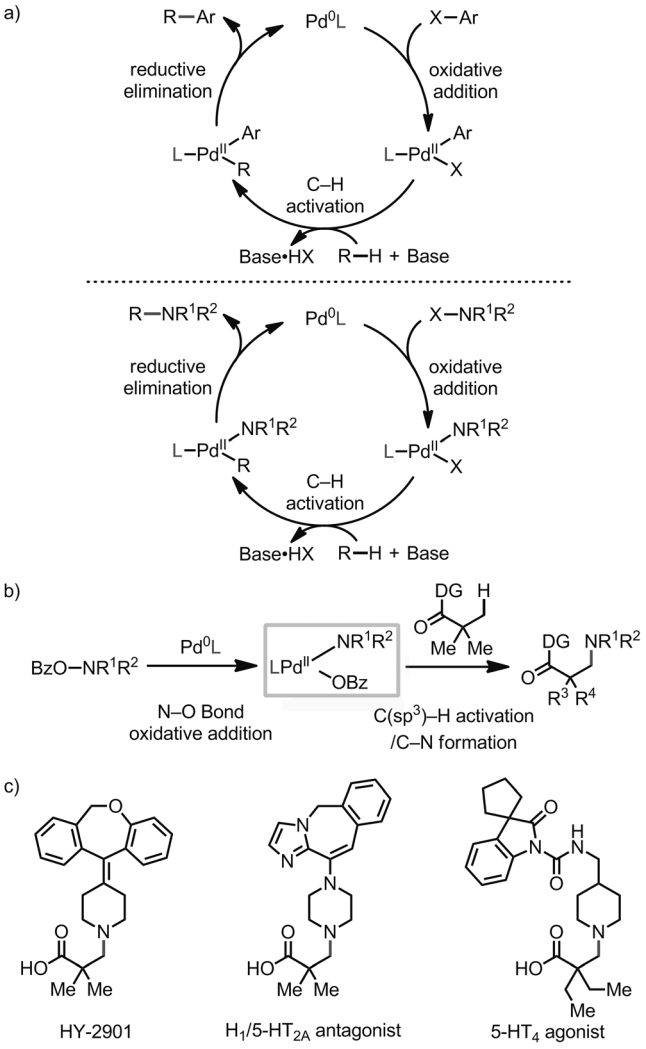
Abstract: *An intermolecular C(sp^3)–H amination using a Pd^0/PAr_3 catalyst was developed. The reaction begins with oxidative addition of R_2N–OBz to a Pd^0/PAr_3 catalyst and subsequent cleavage of a C(sp^3)–H bond by the generated Pd–NR_2 intermediate. The catalytic cycle proceeds without the need for external oxidants in a similar manner to the extensively studied palladium(0)-catalyzed C–H arylation reactions. The electron-deficient triarylphosphine ligand is crucial for this C(sp^3)–H amination reaction to occur.*

The development of C–N bond-forming reactions involving transition-metal-catalyzed C–H activation is of great importance,[1,2] as alkylated nitrogen-containing compounds are prevalent in biologically active natural products and widely used in modern drug discovery.[3] Despite recent efforts in the development of directed intermolecular C(sp^2)–H amidation and amination reactions using various metal catalysts,[4–9] only a few examples of directed intermolecular C(sp^3)–H activation/C–N bond formation have been reported using palladium[10] or iridium catalysts.[11] Inspired by the palladium(0)-catalyzed C–H arylation reaction with aryl halides (Ar–X),[12] we questioned whether we could use O-benzoyl hydroxylamines or N-chloroamines (R^1R^2N–X) in place of Ar–X species to develop an analogous catalytic cycle as a new avenue for intermolecular C(sp^3)–H amination (Scheme 1a). Herein, we report the first example of a Pd^0/PAr_3-catalyzed intermolecular amination of C(sp^3)–H bonds in aliphatic amides to install an alkylamine moiety at the β-position (Scheme 1b). Notably, the previously reported C(sp^3)–H amidation reaction[10a] does not permit the introduction of an alkyl amine moiety. This new catalytic cycle is initiated by oxidative addition of O-benzoyl hydroxylamines to Pd^0, and regenerates the Pd^0 catalyst through C–N reductive elimination without the need for external oxidants. The use of an electron-deficient phosphine ligand is crucial for this reaction to proceed. This β-C(sp^3)–H amination of aliphatic acids provides a new method for the synthesis of bioactive β-amino acids (Scheme 1c).[13–15]

We have recently developed palladium(0)-catalyzed intermolecular C(sp^3)–H arylation and alkynylation reactions promoted by phosphine and N-heterocyclic carbene (NHC) ligands.[16,17] However, development of analogous redox catalysis using amine coupling partners to achieve C(sp^3)–H amination has not been successful to date. Recently, an intramolecular C(sp^2)–H amination involving a Pd^0/Pd^{II} catalytic cycle has been reported.[18] This reaction starts with the oxidative addition of the N–O bond of the tethered oxime ester to Pd^0. While this study is inspiring, the use of an external N–O coupling partner to perform intermolecular



Scheme 1. Design of a catalytic cycle for intermolecular C(sp^3)–H amination. a) Analogy to palladium(0)-catalyzed C–H arylation without using external oxidants. b) Ligand-promoted intermolecular C(sp^3)–H amination. c) Biologically active β-amino acids. Bz = benzoyl, DG = directing group.

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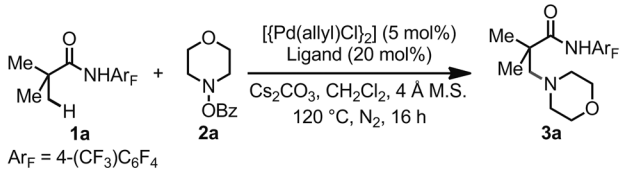
[**] We gratefully acknowledge The Scripps Research Institute and NSF under the CCI Center for Selective C–H Functionalization, and CHE-1205646 for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201502075.

C(sp^3)–H amination is a distinct challenge. We initiated our investigation into the palladium(0)-catalyzed C(sp^3)–H amination of the amide **1a** (for structure see Table 1), as the weakly coordinating N-arylamide auxiliary has been shown to be able to direct Pd^0/PAr_3-catalyzed C(sp^3)–H arylation and alkynylation.[16,17] We selected O-benzoyl hydroxylmorpholine (**2a**) as the aminating reagent,[4c,7b] which can be readily prepared using a known procedure.[19] We anticipated that oxidative addition of **2a** to Pd^0 could occur in the presence of phosphine ligands. However, identification of suitable ligands and reaction conditions to ensure that the L_nPd^{II}–NR_2 species would be able to coordinate with the amide substrate and subsequently activate the β-C(sp^3)–H bonds presents a significant challenge.

Our early experimentation employed the commonly used combination of $Pd(OAc)_2$ and triphenylphosphine as the precatalyst to explore reaction conditions that would lead to the formation of the amination product. We found the reaction of **1a** with amine coupling partner **2a** in the presence of this precatalyst and Cs_2CO_3 in dichloromethane at 120 °C gave the desired amination product **3a** in 10 % yield (Table 1, entry 1). Through extensive screening of palladium sources and bases, we identified [{Pd(allyl)Cl}$_2$] to be the most effective precatalyst, thus affording **3a** in 15 % yield (entry 2). The yield decreased to 5 % when the reaction was carried out in the absence of triphenylphosphine (entry 3).

Table 1: Ligand optimization for C(sp^3)–H amination.[a,b]



Entry	Ligand	Yield [%]
1[c]	PPh_3	10
2	PPh_3	15
3	–	5
4	IAd·HBF_4	5
5	PCy_3·HBF_4	2
6	*t*BuXPhos·HBF_4	3
7	$P(4\text{-}FC_6H_4)_3$	28
8	$P(4\text{-}CF_3C_6H_4)_3$	41
9	PAr_3	83
10	PAr_2Ph	39
11	$PAr_2(2,6\text{-}F_2C_6H_3)$	12
12	$PAr_2(2\text{-}CF_3C_6H_4)$	24
13	$PAr_2(3\text{-}CF_3C_6H_4)$	72
14	$PAr_2(4\text{-}CF_3C_6H_4)$	46
15[d]	$1,2\text{-}(PAr_2)_2C_6H_4$	0
16	$OPAr_3$	3

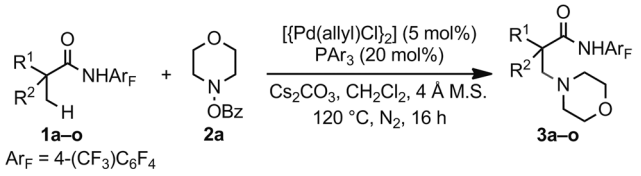
[a] Experiments were performed with **1a** (0.1 mmol), **2a** (0.4 mmol), [{Pd(allyl)Cl}$_2$] (0.005 mmol), ligand (0.02 mmol), Cs_2CO_3 (0.4 mmol), and 4 Å molecular sieves (M.S.; 50 mg) in CH_2Cl_2 (1.5 mL) for 16 h at 120 °C under N_2 atmosphere. [b] The yield was determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as the internal standard. [c] $Pd(OAc)_2$ (0.01 mmol) was used. [d] The bidentate ligand (0.01 mmol) was used. Ar = 3,5-$(CF_3)_2C_6H_3$.

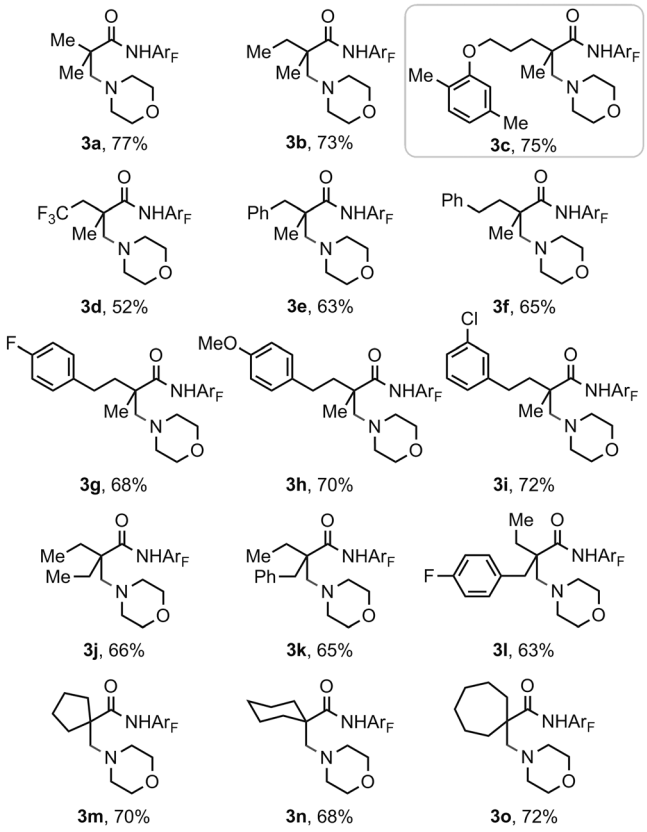
The observed significant ligand effect prompted us to screen various phosphine and NHC ligands which have been previously used for palladium(0)-catalyzed coupling reactions. Somewhat surprisingly, the optimal electron-rich NHC and phosphine ligands for our previous C(sp^3)–H arylation and alkynylation reactions[16,17] proved to be ineffective for this C(sp^3)–H amination (entries 4–6). These results indicate that the required ligand properties of the L_nPd^{II}–NR_2 intermediate for cleaving the C(sp^3)–H bonds may be different from L_nPd^{II}–aryl and L_nPd^{II}–alkynyl species. We therefore began to investigate electron-deficient phosphine ligands (entries 7–9; for detailed ligand screening see the Supporting Information). We found that tris(4-fluorophenyl)phosphine improved the yield to 28 % (entry 7). Replacement of the fluorine by the more electron-withdrawing trifluoromethyl group in the phosphine ligand led to further improvement, thus affording **3a** in 41 % yield (entry 8). Remarkably, when we utilized the tris[3,5-bis(trifluoromethyl)phenyl]phosphine ligand, the reaction proceeded to give **3a** in 83 % yield (entry 9). Although further modification of triarylphosphine ligands did not improve this reaction (entries 10–14), these experiments provided further insights into the ligand effect: 1) electron-withdrawing substituents on the aryl groups were crucial to the reactivity (entry 10); 2) substitution at the 2-position of the aryl ring was detrimental to the reaction (entries 11 and 12); 3) electron-withdrawing groups at 3-positions are more effective than those at the 4-position of the aryl ring (entries 13 and 14); 4) monodentate, rather than bidendate ligands, are required for this reaction (entry 15). The control experiment also illustrated that triarylphosphine oxides were ineffective for promoting the reaction, thus confirming that the triarylphosphine is the active ligand (entry 16).

Amides derived from various aliphatic acids were subjected to these optimized reaction conditions (Table 2). Amination of **1a** and **1b** provided the corresponding products **3a** and **3b** in 77 and 73 % yields, respectively. The amide **1c** of the parent drug gemfibrozil was also aminated to give **3c** in 75 % yield. The amination of the amide **1d** afforded a valuable β-amino-acid derivative containing a trifluoromethyl group (**3d**) in 52 % yield. A variety of aryl groups on the β- and γ-positions were well tolerated (**3e–i**). In comparison to other β-C(sp^3)-H functionalization reactions, this amination protocol displays exclusive monoselectivity in the presence of two or three α-methyl groups (**1a–i**). The newly installed amino group appears to prevent palladium catalysts from activating the remaining methyl groups through bidentate coordination. Amides containing a single α-methyl group are also reactive, thus affording the desired amination products in good yields (**3j–o**). Substrates containing α-protons are incompatible with the reaction conditions, presumably because the basic L_nPd^{II}–amido species generated in situ will react with the acidic α-carbon center.

Intriguingly, aminating reagents derived from pyrrolidine and acyclic dialkylamines were not effective coupling partners and resulted in poor yields. Encouragingly, batchwise addition of the more challenging amine coupling partners improved the reaction yield from 14 to 27 % (see the Supporting Information). We thus explored the scope of the

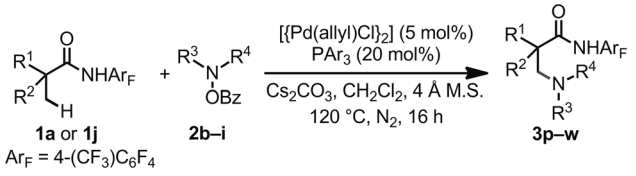
Table 2: The β-C(sp³)–H amination of aliphatic acid derivatives.[a,b]

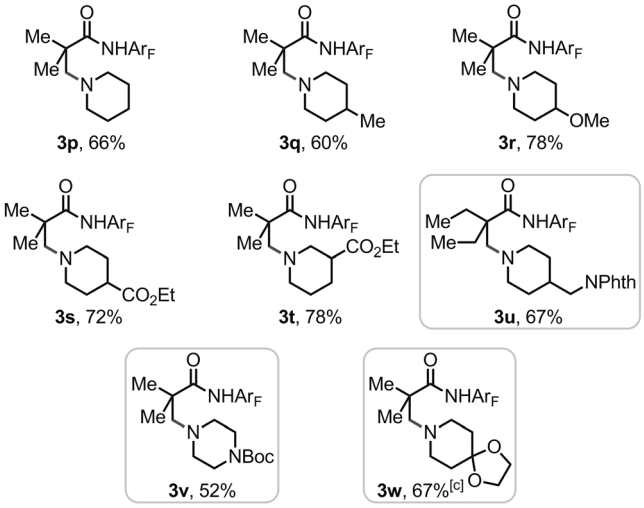




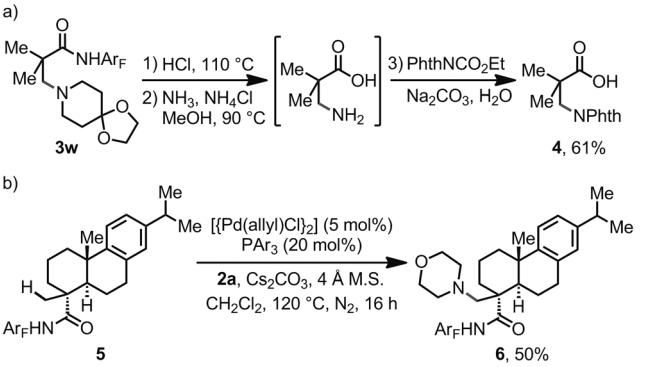
[a] Experiments were performed with **1a–o** (0.1 mmol), **2a** (0.4 mmol), [{Pd(allyl)Cl}$_2$] (0.005 mmol), P[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_3$ (0.02 mmol), Cs_2CO_3 (0.4 mmol), and 4 Å molecular sieves (50 mg) in CH_2Cl_2 (1.5 mL) for 16 h at 120 °C under N_2 atmosphere. [b] Yields of isolated products.

Table 3: Scope of amine reagents for C(sp³)–H amination.[a,b]





[a] Experiments were performed with **1a** or **1j** (0.1 mmol), **2b–l** (0.4 mmol), [{Pd(allyl)Cl}$_2$] (0.005 mmol), P[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_3$ (0.02 mmol), Cs_2CO_3 (0.4 mmol), and 4 Å molecular sieves (50 mg) in CH_2Cl_2 (1.5 mL) for 16 h at 120 °C under N_2 atmosphere. [b] Yields of isolated products. [c] [{Pd(allyl)Cl}$_2$] (0.0075 mmol), P[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_3$ (0.03 mmol), and CH_2Cl_2 (2.0 mL) were used.

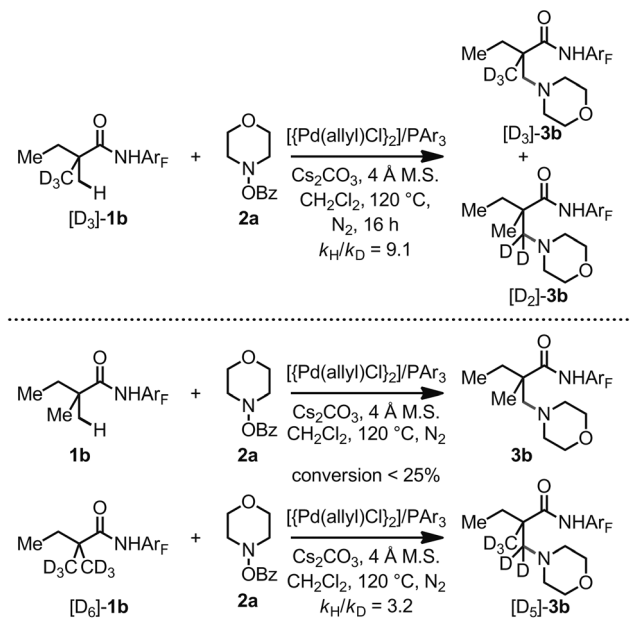


Scheme 2. Applications of C(sp³)–H amination. a) Synthesis of N-Phth-protected β-amino acids. b) Late-stage functionalization of a dehydroabietic acid derivative.

medicinally important piperidine coupling partners (Table 3). A variety of functional groups on the piperidines were well tolerated, including ethers, esters, and phthalimido (Phth)-protected amino groups (**3r–u**). Notably, the amination product **3u** is a key precursor for the synthesis of the 5-HT$_4$ agonist shown in Scheme 1c.[15] The literature procedure for the synthesis of this agonist suffered from a lengthy synthetic sequence and low yield. We were pleased to find that the aminating reagent derived from piperazine was also compatible with this reaction (**3v**). The amination product **3v** is a key synthetic intermediate of a H_1/5-HT$_{2A}$ antagonist.[14] Amination of **1w** with a piperidinone-derived coupling partner was carried out to give **3w** in 67% yield, and it could be utilized to synthesize the biologically active compound HY-2901.[13]

To access a wider range of β-amino acids using this newly developed protocol, the piperidone unit in the amination product **3w** was subsequently deprotected to reveal the free amino group by using a previously established procedure (Scheme 2a).[20] The free amino acid was then converted into the Phth-protected β-amino acid **4** and isolated in 61% yield over three steps. This amination reaction was also successfully applied to the late-stage functionalization of the substrate **5**, derived from dehydroabietic acid, to synthesize a complex β-amino acid (**6**).

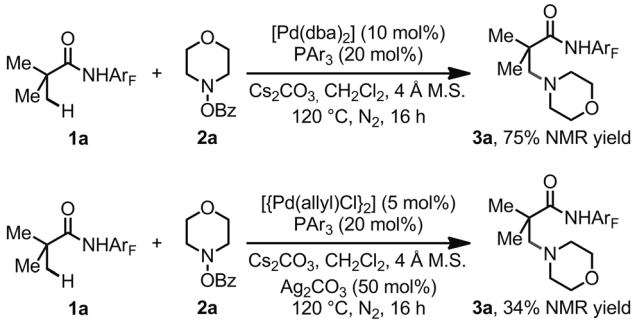
To gain insight into the reaction mechanism, we measured both intra- and intermolecular kinetic isotope effects (KIEs)



Scheme 3. Kinetic isotope effects.

(Scheme 3). The observed intermolecular KIE suggests that C–H cleavage is the rate-limiting step in this C(sp^3)–H amination reaction.

While concrete experimental evidence for the involvement of Pd^0/Pd^{II} instead of Pd^{II}/Pd^{IV} redox chemistry remains to be obtained, a number of key observations made in this reaction are in favor of the former. First, the commonly used Pd^{II} sources for Pd^{II}/Pd^{IV} catalysis such as $Pd(TFA)_2$ (not readily reduced to Pd^0) are not effective (see the Supporting Information). In contrast, the well-known Pd^0 sources, [{Pd(allyl)Cl}$_2$] and [Pd(dba)$_2$], afforded excellent yields (Scheme 4). Second, no external oxidant is required to



Scheme 4. Mechanistic investigations of the catalytic cycle. dba = dibenzylideneacetone.

initiate the reaction when the Pd^0 catalyst is used, a result which is also inconsistent with a Pd^{II}/Pd^{IV} catalytic cycle. In fact, the Ag^I salts that promote arylation by Pd^{II}/Pd^{IV} catalysis inhibit these reactions. For example, the use of Ag_2CO_3 decreased the yield to 34% (Scheme 4). Finally, the previously isolated crystal structure obtained from the oxidative addition of an oxime ester ($R_2C{=}N{-}OCOC_6F_5$) to Pd^0 also lends additional evidence in support of Pd^0/Pd^{II} catalysis.[18] With these considerations in mind, we propose a Pd^0/Pd^{II} catalytic cycle analogous to the intermolecular arylation reaction (Figure 1).[16] Oxidative addition of the O-benzoyl

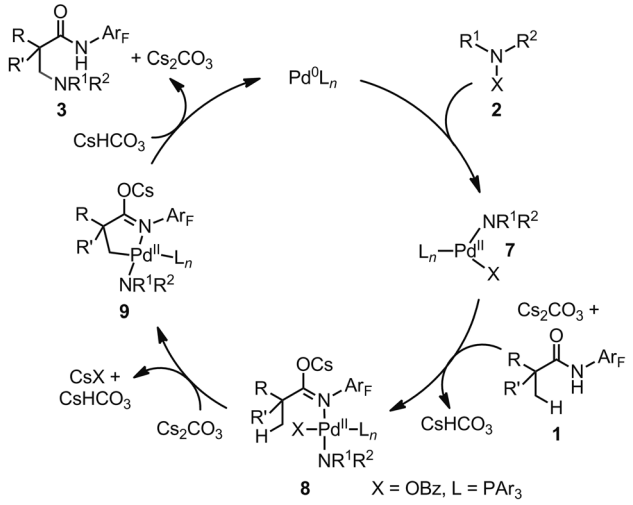


Figure 1. Plausible mechanism of C(sp^3)–H amination.

hydroxylamine **2** to the Pd^0L_n species yields the L_nPd^{II}–amido intermediate **7**, which coordinates to **1** under basic conditions to provide the complex **8**. A similar coordination mode of the imidate was characterized by X-ray crystallography in our previous *ortho*-C(sp^2)–H trifluoromethylation reaction.[21] After C–H cleavage, the palladacycle **9** undergoes reductive elimination to yield the product **3** with concomitant regeneration of Pd^0L_n. The role of the triarylphosphine ligand in this catalytic cycle may be multifaceted. For example, the electron-deficient triarylphosphine ligand is known to stabilize palladium–amido bonds though π back-bonding interactions,[22] thus preventing decomposition of **7**, a step which is essential for C–H activation to occur. It is also likely that this π back-bonding interaction may promote C–N reductive elimination.

In conclusion, we have established a Pd^0/Pd^{II} catalytic cycle to achieve intermolecular C(sp^3)–H amination using an electron-deficient triarylphosphine ligand. The redox chemistry closely resembles palladium(0)-catalyzed C–H arylation with aryl halides, and requires no external oxidants. This transformation provides access to novel β-amino acids including synthetic precursors for several bioactive molecules. Further development of more-efficient ligands to expand the substrate scope is ongoing in our laboratory.

Keywords: amination · amino acids · C–H activation · palladium · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 6545–6549
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Received: March 4, 2015
Published online: April 14, 2015

