Aryl–Nitrogen Coupling Reactions

DOI: 10.1002/anie.200700288

Phenanthroline Ligands in Aryl Palladium Hydrazinato Complexes: Catalysts for Efficient Coupling of Azo Componds with Aryl Boronic Acids**

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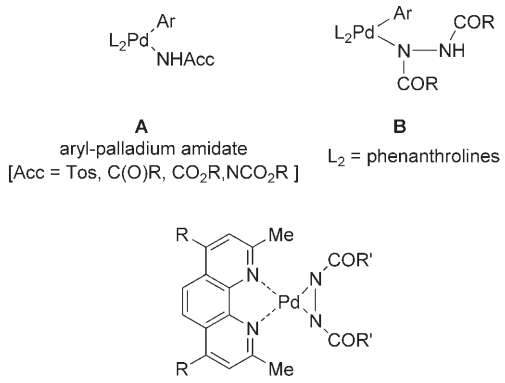
Dedicated to Professor Ekkehart Winterfeldt on the occasion of his 75th birthday

Palladium-catalyzed coupling reactions have a strong standing in modern synthesis. In addition to the extensively developed methodology of carbon–carbon bond formation,[1] additional protocols for carbon–heteroatom bond formation have emerged over the last decade.[2] In particular, the Buchwald–Hartwig coupling synthesis of aniline derivatives through the coupling of amines with aryl halogenides, triflates, and tosylates displays a broad applicability,[3,4] and has recently been extended from coupling reactions with aryl groups to the corresponding vinyl derivatives.[5]

While the reaction has achieved a highly advanced stage for common amines, related Pd-catalyzed coupling reactions of amides remain the topic of ongoing investigation. In particular, the formation of aryl palladium amidate complexes **A** (Scheme 1) as immediate precursors for the reductive elimination of N-aryl amides constitutes a major problem in the realization of catalytic reactivity. Catalytic experiments from Yin and Buchwald[6] and stoichiometric studies from Hartwig and co-workers[7] that employed 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (xantphos) complexes have recently shown that temperatures of up to 110 °C are required for this step. Herein, we describe the successful realization of a catalytic aryl–nitrogen bond formation from palladium amidate complexes **B** that bear phenanthroline-type ligands.

Recently, we synthesized the novel palladadiaziridine structures **1a–c** and identified them as key intermediates in a catalytic homogeneous reduction of azo compounds in which the protonolysis of the Pd–N bond is the key step.[8] In the extension of the investigation on the reaction behavior of palladadiaziridines we envisioned that the Pd–N–N three-membered ring in the complexes **1** should react with one equivalent of phenyl boronic acid or phenyl tributylstannane to yield a phenylated palladium η^1-hydrazinato compound **B**. This complex should then be able to undergo reductive nitrogen–carbon bond formation to yield arylated hydrazines. It should next be possible to regenerate the original complex **1** from the resulting palladium(0) complex upon coordination of the appropriate azo dicarbonyl compound.[8] In this way the development of a general catalytic transformation of azodicarboxylates into arylated hydrazines via aryl palladium amidates, and hence an extension of N–N multiple-bond functionalization should be possible.[9,10] Indeed, this concept proved viable in the development of a new catalysis process.



Scheme 1. Aryl palladium amidato complexes **A** and **B** as key intermediates and palladadiaziridines **1a–f**.

After some experimentation, we found that catalytic phenylation of free azodicarboxylates could indeed be achieved in high yields in the presence of 5 mol% of the preformed palladadiaziridine **1** as catalyst and with 1,2-dichloroethane as solvent (Table 1). The choice of an aprotic solvent proved important, with 1,2-dichloroethane giving the best results. A temperature of 60 °C already gave the complete conversion within 12 h. Notably, the reaction could even proceed at room temperature, although slightly longer reaction times (20 h) were required. When the catalyst

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[**] This work was generously supported from the Fonds der Chemischen Industrie, the DFG (SFB 624), and the Otto-Röhm-Gedächtnisstiftung. A.I. is grateful to Fundación La Caixa and DAAD for a predoctoral fellowship.

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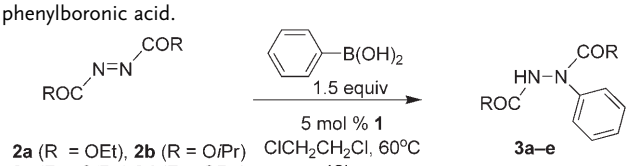
Table 1: Palladium-catalyzed coupling of azodicarboxylate esters with phenylboronic acid.



2a (R = OEt), **2b** (R = O*i*Pr)
2c (R = O*t*Bu),**2d** (R = OBn)
2e (R = 1-piperidinyl)

3a–e

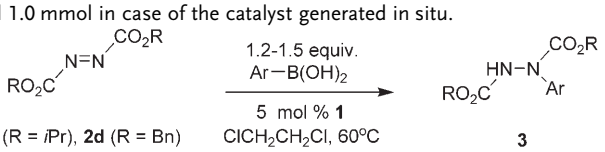
Substrate	Product	Yield [%][a]
2a	**3a**	92 (88)
2b	**3b**	97 (94)
2b[b]	**3b**	98
2b[c]	**3b**	97 (90)
2b[d]	**3b**	98 (94)
2c	**3c**	82 (78)
2d	**3d**	94 (94)
2e	**3e**	88

[a] Yield of the isolated product at quantitative conversion (>99% product formation of **3** according to GC). Yields are based on 1 mmol reactions and are calculated for 1.05 mmol maximum yield. Values in brackets refer to reactions at RT. [b] Reaction with 1 mol% catalyst (maximum yield 1.01 mmol). [c] Reaction with catalyst formed in situ from [(bathocuproine)Pd(dba)] (maximum yield 1 mmol). [d] Reaction with [(neocuproine)Pd{N_2(CO*i*Pr)$_2$}] (**1f**).

loading was reduced to 1 mol%, the product was still formed quantitatively after 48 h. The palladadiaziridine catalyst could be generated in situ from [(bathocuproine)Pd(dba)] (dba = *trans*,*trans*-dibenzylideneacetone) without loss of reactivity. This introduces readily available catalysts from easily accessible precursors without the need for isolation of the complexes **1**. The neocuproine-based palladium catalyst **1f** proved equally efficient. The new amide derivative **1e** also induced a clean reaction and extends the scope of both the synthesis of palladadiaziridines, and of the catalysis to give urea derivatives.

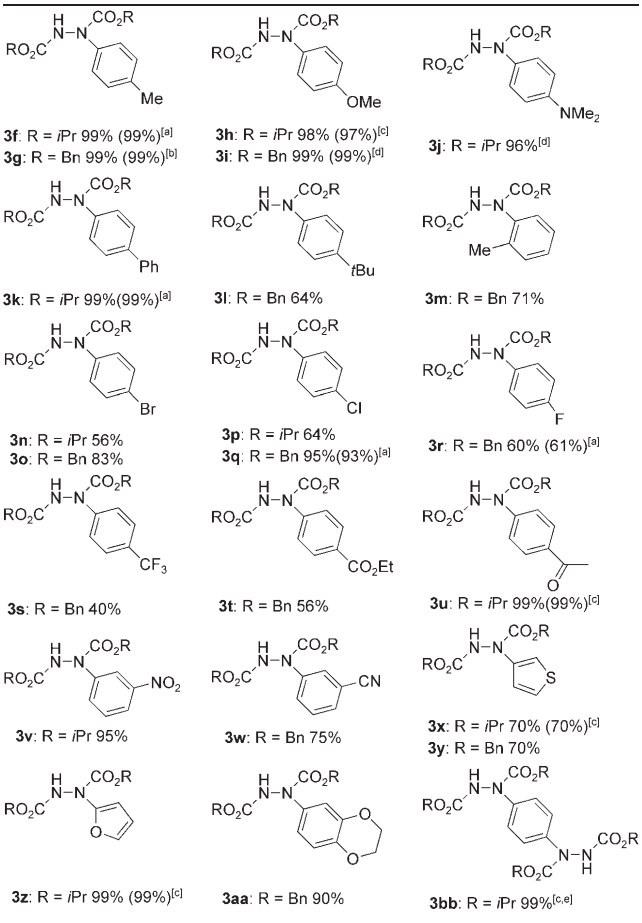
The observed reactivity was based to a large extent on the use of the phenanthroline ligands bathocuproine and neocuproine.[11,12] Standard bisphosphine- or monophosphine-ligated or NHC-derived palladium complexes (NHC = N-heterocyclic carbene) proved to be completely inefficient and induced the formation of biphenyl. The reaction proved general under the given conditions. Table 2 displays an overview for the arylation of azo derivatives with the three representative palladadiaziridine catalysts **1b**, **1d**, and **1f**, which effected the selective aryl transfer under the standard conditions. The two esters **2b** and **2d** were selected as the azo compounds, and the benzyl derivative usually gave the better yields. With regard to the aryl group, 18 additional aromatic groups other than phenyl were screened, which included an *ortho*-substitution pattern, all of which reacted in good to excellent yields. Electron-donating substituents usually lead to faster reactions and can occur already at room temperature. Apart from electron-rich and -neutral substituents, aryl groups that bore halogens, electron-demanding substituents in the *meta* and *para* positions, as well as heterocycles such as thiophene and furane were well accepted. When the 1,4-phenyl diboronic acid was used, the dicoupled product **3bb** was yielded quantitatively using DMF as the solvent because

Table 2: Products of the palladium-catalyzed coupling of azodicarboxylate esters with aryl boronic acids. All reactions were carried out on a 1 mmol scale. The given yields refer to isolated material at quantitative conversion (>99% product formation of **3** according to GC) and are calculated based on 1.05 mmol maximum yield for preformed catalysts and 1.0 mmol in case of the catalyst generated in situ.



2b (R = *i*Pr), **2d** (R = Bn)

3



3f: R = *i*Pr 99% (99%)[a]
3g: R = Bn 99% (99%)[b]

3h: R = *i*Pr 98% (97%)[c]
3i: R = Bn 99% (99%)[d]

3j: R = *i*Pr 96%[d]

3k: R = *i*Pr 99%(99%)[a]

3l: R = Bn 64%

3m: R = Bn 71%

3n: R = *i*Pr 56%
3o: R = Bn 83%

3p: R = *i*Pr 64%
3q: R = Bn 95%(93%)[a]

3r: R = Bn 60% (61%)[a]

3s: R = Bn 40%

3t: R = Bn 56%

3u: R = *i*Pr 99%(99%)[c]

3v: R = *i*Pr 95%

3w: R = Bn 75%

3x: R = *i*Pr 70% (70%)[c]
3y: R = Bn 70%

3z: R = *i*Pr 99% (99%)[c]

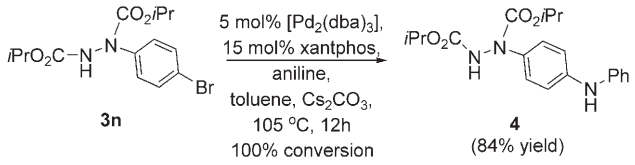
3aa: R = Bn 90%

3bb: R = *i*Pr 99%[c,e]

[a] With catalyst generated in situ. [b] Reaction at RT. [c] With neocuproine-derived catalyst **1f**. [d] Reaction time of 3 h. [e] In DMF as solvent; diboronic acid/**2b** = 1/2.2

of solubility issues. Overall, the coupling reactions are characterized by complete selectivity, high yields, and mild reaction conditions without the need for absolute conditions. Additionally, the reactions could generally be carried out under base-free conditions, hence minimizing the formation of waste salts.

For 4-chloro- and 4-bromophenylboronic acid, the respective aryl–halogen bond remained intact during the catalysis, which demonstrates that a potential Buchwald–Hartwig coupling cannot compete under the present conditions of phenanthroline–palladium catalysis. A conventional Buchwald–Hartwig reaction of **3n** using a xantphos–Pd catalyst[14] gave exclusive aniline coupling to yield the 1,4-diaminobenzene derivative **4** (Scheme 2). This result exemplifies the



Scheme 2. Buchwald–Hartwig coupling with product **3n**.

dominating role of the nature of the chelating ligand on the course of the coupling reaction and enables a defined differentiation of reactivity.

A catalytic cycle for the mechanistic understanding of this new C–N bond formation from azodicarboxylates and aryl boronic acids is suggested in Figure 1a. The reaction is initiated by aryl transfer from the boronic acid to the palladium center with concomitant opening of the palladadiaziridine, thus leading to the formation of complex **B**. A reductive elimination of the monoarylated hydrazine **3** from the amidato complex **B** generates the corresponding palladium(0) complex **C**. The spontaneous character of this process is of particular significance in view of the mentioned difficulties in sp^2-carbon–amide coupling reactions in traditional Buchwald–Hartwig reactions. In addition, no hydrazine-exchange processes take place at stage **B** under the chosen conditions, since the formation of *N*,*N*′-bisarylated hydrazines was not observed in any case, which suggests that **B** is a short-lived intermediate. Preliminary mechanistic NMR studies on the reaction of **1f** with 10 equivalents of aryl boronic acid under the catalysis conditions (30 °C, $c = 0.2$ M) in tetrachloroethane show a clean conversion to compound **3h** within 2 h. The intermediate complex **B** was not observed under these conditions, which again suggests that the reductive elimination of **3** from **B** proceeds extremely rapidly.[15]

The palladadiaziridine is finally regenerated from complex **C** through coordination of free azodicarboxylate, which apart from its role as precursor to the hydrazide product, serves as a reoxidant. This use represents a significant step forward in comparison to related coupling reactions such as the oxidative Heck reaction between boronic acids and alkenes, in which the reoxidation with molecular oxidant requires further additives.[16]

In summary, we have described a selective protocol, which is mild and side-product free, for the coupling of aryl boronic acids and azo compounds to provide *N*-aryl hydrazines. The key step of the catalysis consists of the first general reductive carbon–nitrogen bond formation from palladium amidate complexes. The course of this reaction strongly depends on the nature of the ligand, and phenanthroline-type ligands are presently unchallenged. We expect that this class of ligands will find broader applicability in the direct functionalization of amides and are currently being investigated in potential reactions.

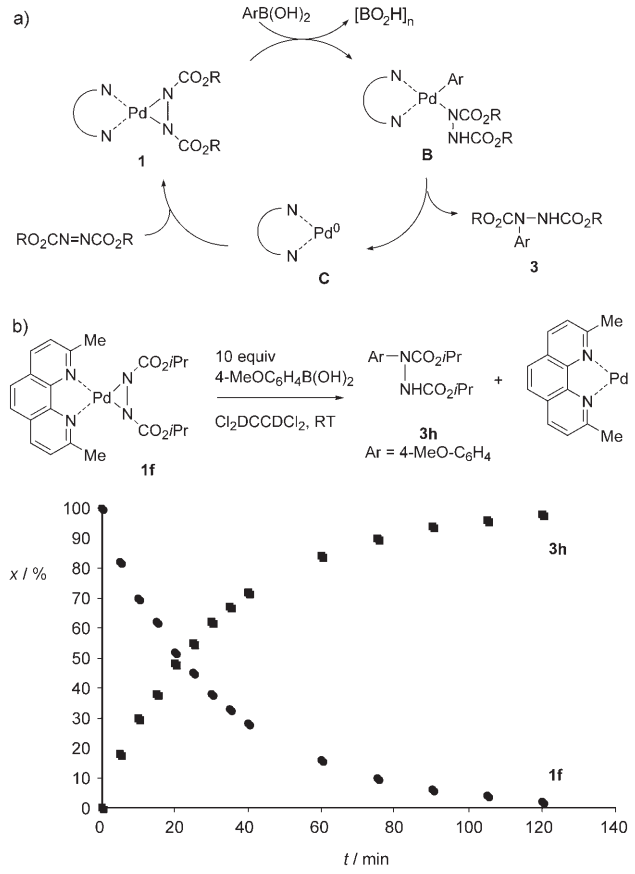


Figure 1. a) Catalytic cycle for palladium-catalyzed coupling between aryl boronic acids and azodicarboxylates, and b) monitoring by NMR spectroscopy of the standard reaction of **1f** to give **3h**.

Received: January 22, 2007
Revised: May 15, 2007
Published online: July 19, 2007

Keywords: amides · aryl boronic acids · coupling reactions · hydrazines · palladium

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