ORGANIC LETTERS

2011
Vol. 13, No. 23
6308–6311

Palladium-Catalyzed C–C Bond Formation of Arylhydrazines with Olefins via Carbon–Nitrogen Bond Cleavage

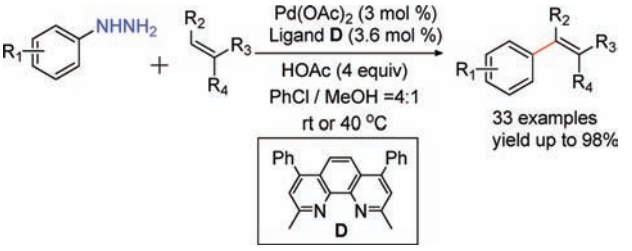
Ming-Kui Zhu, Jun-Feng Zhao, and Teck-Peng Loh*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371

teckpeng@ntu.edu.sg

Received October 24, 2011

ABSTRACT



The unactivated carbon–nitrogen bond of various aryl hydrazines was cleaved under very mild conditions by Pd(0) with the assistance of Pd(II). The in situ generated aryl palladium complex readily takes part in the C–C bond formation with olefins. This study offered a new mode of C–Pd bond formation, which will spur the development of palladium-catalyzed cross-coupling in the future.

Palladium-catalyzed cross-coupling reactions via selective cleavage of unreactive bonds such as carbon–hydrogen,[1] carbon–carbon,[2] and carbon–nitrogen[3] bonds are versatile and powerful tools for organic chemists because they provide unique organic transformations which are difficult to be carried out using other methods. Among these strategies, the cross-coupling reaction involving carbon–nitrogen bond cleavage is the least explored, especially for the nonreactive carbon–nitrogen bond.[3] Generally, the carbon–nitrogen bonds are activated by conversion to diazonium salts,[3a–c] ammonium salt,[3d–f] or aza heterocycles.[3g,h] However, existing methods are still plagued with problems such as limited substrate scope, harsh reaction conditions, the explosive and unstable nature of the substrates, the need to use strong acids and an air-sensitive nickel catalyst, etc. In view of this, there is still a need to develop new methods to cleave carbon–nitrogen bonds. Recently, Kakiuchi and co-workers developed a carbon–carbon bond formation strategy via the ruthenium-catalyzed unactivated carbon–nitrogen bond cleavage of anilines.[4] However, as far as we know the transition-metal-catalyzed cleavage of carbon–nitrogen bonds in arylhydrazine has not been reported.[5]

(1) For reviews, see: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826–834. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1770. (c) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318–5365. (d) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (f) Bras, J. L.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170–1214.

(2) For decarboxylative coupling reaction, see: (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250–11251. (b) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323–10333. (c) Goossen, L. J.; Deng, G. J.; Levy, L. M. *Science* **2006**, *313*, 662–664. (d) Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103–7106. (e) Goossen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833. (f) Goossen, L. J.; Rodriguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248–15249. (g) Bi, H. P.; Zhao, L.; Liang, Y. M.; Li, C. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 792–795.

(3) For reviews of palladium catalyzed cleavage of activated aromatic C–N bonds, see: (a) Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. *Chem. Rev.* **2006**, *106*, 4622. (b) Felpin, F. X.; Nassar-Hardy, L.; Callonnec, F. L.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815–2831. (c) Taylor, J. G.; Moro, A. V.; Correia, C. R. *Eur. J. Org. Chem.* **2011**, 1403–1428. For selected pioneering work of transition-metal-mediated unactivated carbon–nitrogen bond cleavage, see: (d) Wenkert, E.; Han, A.-L.; Jenny, C.-J. *J. Chem. Soc., Chem. Commun.* **1988**, 975–976. (e) Bonanno, J. B.; Henry, T. P.; Neithamer, D. R.; Wolczanski, P. T.; Lobkovsky, E. B. *J. Am. Chem. Soc.* **1996**, *118*, 5132–5133. (f) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046–6047. (g) Saeki, T.; Son, E.-C.; Tamao, K. *Org. Lett.* **2004**, *6*, 617–619. (h) Liu, J.; Robins, M. *J. Org. Lett.* **2004**, *6*, 3421–3423.

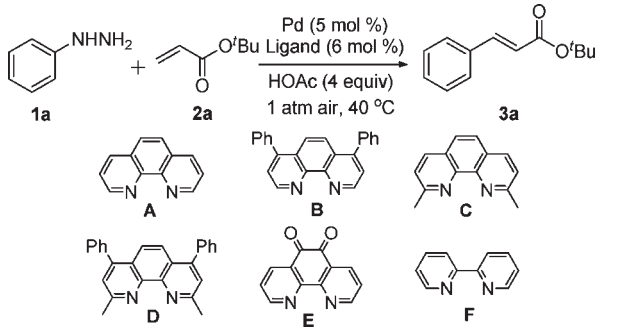
(4) (a) Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098. (b) Koreeda, T.; Kochi, T.; Kakiuchi, F. *J. Am. Chem. Soc.* **2009**, *131*, 7238–7239.

(5) Akiyama, F.; Miyazaki, H.; Kaneda, K.; Teranishi, S.; Fujiwara, Y.; Abe, M.; Taniguchi, H. *J. Org. Chem.* **1980**, *45*, 2359–2361.

10.1021/ol202862t
Published on Web 11/04/2011

Herein we report the first *palladium-catalyzed* C−C bond formation of arylhydrazines via aryl carbon−nitrogen bond cleavage with olefins under very mild conditions.

Table 1. Palladium-Catalyzed Cross-Coupling of Phenylhydrazine (**1a**) with *tert*-Butyl Acrylate (**2a**)[a]



entry	Pd	ligand	solvent	time (h)	yield (**3a**) (%)[b]
1	$Pd(OAc)_2$	No	DCE	4	22%
2	No	No	DCE	4	trace
3	$Pd(OAc)_2$	**A**	DCE	2	68%
4	$PdCl_2$	**A**	DCE	2	61%
5	$Pd(CO_2CF_3)_2$	**A**	DCE	2	57%
6	$Pd(dba)_2$	**A**	DCE	2	41%
7	$Pd(OAc)_2$	**B**	DCE	2	72%
8	$Pd(OAc)_2$	**C**	DCE	2	81%
9	$Pd(OAc)_2$	**D**	DCE	2	83%
10	$Pd(OAc)_2$	**E**	DCE	2	23%
11	$Pd(OAc)_2$	**F**	DCE	2	77%
12[c]	$Pd(OAc)_2$	**D**	PhCl/MeOH	2	91%
13[d]	$Pd(OAc)_2$	**D**	PhCl/MeOH	2	91%
14[e]	$Pd(OAc)_2$	**D**	PhCl/MeOH	2	75%

[a] Unless noted otherwise, the reactions were carried out on a 0.30 mmol scale of **1a** with 4.0 equiv of HOAc (1.2 mmol), and 2.0 equiv **2a** (0.6 mmol) in solvent (0.5 mL). [b] Isolated yield. [c] 50 mg 4 Å MS was added. [d] With 3 mol % $Pd(OAc)_2$. [e] With 1 mol % $Pd(OAc)_2$.

The pioneering work of palladium-mediated unactivated carbon−nitrogen bond cleavage involving arylamine and arylhydrazine had been done by Fujiwara et al. by employing stoichiometric amounts of palladium salts, albeit low reaction efficiency was observed.[5] Their work demonstrated the feasibility of cleavage of an unactivated carbon−nitrogen bond by palladium. However, the mechanism of this reaction is still unclear and there is much room for its improvement. Recently, we are interested in palladium catalyzed aerobic transformations, especially when molecular oxygen or air was used as the sole oxidant.[6] Inspired by Fujiwara's work and based on the development of palladium oxidase catalysis,[7] we envisioned that the catalytic version of this reaction might be realized by the combination of Pd(II)-catalyzed C−C bond formation and ligand assisted dioxygen-coupled reoxidation of Pd(0).

Initially, aniline was chosen as the cross-coupling partner and treated with the *tert*-butyl acrylate in the presence of 5 mol % of $Pd(OAc)_2$, 6 mol % of ligand **A** (1,10-phenanthroline), and 5 equiv of HOAc in open air. However, no desired cross-coupling product involving C−N bond cleavage was observed (see Supporting Information). Interestingly, the target cross-coupling product was obtained in 68% yield when phenylhydrazine was treated under the same conditions (Table 1, entry 3).

With this encouraging result in hand, we evaluated other palladium(II) salts as well as palladium(0) complexes and found that $Pd(OAc)_2$ offered the best yield. Further investigation demonstrated that the ligand plays an important role in the reaction (Table 1). Both air and acetic acid are crucial for the reaction because no reaction was observed in the absence of either of them. This transformation proceeded smoothly at room temperature although higher efficiency was observed at 40 °C. Solvent also had some effect on the reaction, and we found that a mixture of PhCl and MeOH is the optimal choice of solvent (for the details of reaction condition optimization, see Supporting Information). The catalyst loading could be decreased to 3 mol % without any loss of the yield, and it could be further decreased to 1 mol % with a slightly decreased yield (Table 1, entry 14). Finally, the best result was obtained with 3 mol % of $Pd(OAc)_2$ and 3.6 mol % of ligand **D** as the catalyst and a mixture of PhCl and MeOH as the solvent under air.

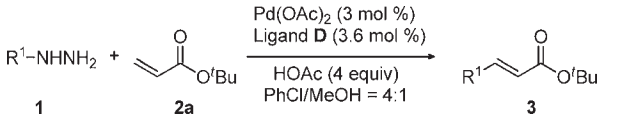
The generality of this novel process was explored with various arylhydrazines under the optimal reaction conditions, and the results are summarized in Table 2. As already outlined, a wide range of arylhydrazines gave the desired products in good yields, including *ortho*-, *para*-, and *meta*-substituted arylhydrazines. Both the electron-withdrawing and -donating groups on the *para*-substituted aromatic hydrazines are tolerated (Table 2, entries 2−11). Generally, electron-poor arylhydrazines are more reactive than electron-rich ones. A longer reaction time was required to get the product in good yield when an electron-donating group was present in the substrates (Table 2, entries 2, 17). The electron-poor 4-hydrazinylbenzoic acid (**1i**) gave an almost quantitative yield at room temperature (Table 2, entry 9). The *ortho*-substituted arylhydrazines also proceeded readily to give the cross-coupling product in good yields (Table 2, entries 15, 16, 20). The tolerance of *ortho*-substituted arylyhydrazines is an advantage over the palladium-catalyzed diazonium salts chemistry, which is frequently sensitive to steric hindrance. It is notable that excellent chemoselectivities were observed when chloro- (Table 2, entries 4, 18, 19), bromo- (Table 2, entries 6 and 13), and iodophenylhydrazine (Table 2, entry 7) were involved in this coupling reaction. This feature affords an

(6) (a) Zhu, M. K.; Zhao, J. F.; Loh, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 6284–6285. (b) Xu, Y. H.; Lu., J.; Loh, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 1372–1373. (c) Zhou, H.; Xu, Y. H.; Chung, W. J.; Loh, T. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 5355–5358. (d) Feng, C.; Loh, T. P. *J. Am. Chem. Soc.* **2010**, *133*, 17710–17712.

(7) (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420 and the references cited therein. (b) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188–7189.

opportunity for further selective functionalization at the halide group. The carboxylic acid and sulfonamide groups on the aromatic ring are also compatible and these substrates were more reactive owing to their electron deficiency (Table 2, entries 9, 11, 14).

Table 2. Palladium-Catalyzed Cross-Coupling of Various Arylhydrazines with *tert*-Butyl Acrylate (**2a**)[a]



1 2a 3

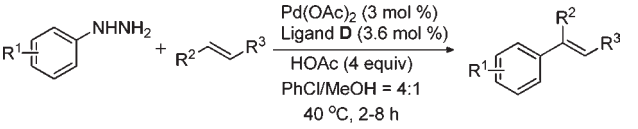
entry	R^1	temp (°C)	time (h)	yield (%)[b]
1	Ph(**1a**)	40	2	91% (**3a**)
2	4-MeO-C_6H_4 (**1b**)	40	6	90% (**3b**)
3	4-Me-C_6H_4(**1c**)	40	2	92% (**3c**)
4	4−F-C_6H_4(**1d**)	40	2	85% (**3d**)
5	4-Cl-C_6H_4 (**1e**)	40	2	85% (**3e**)
6	4-Br-C_6H_4 (**1f**)	40	2	81% (**3f**)
7	4-I-C_6H_4 (**1g**)	25	10	80% (**3g**)
8	4-CN-C_6H_4 (**1h**)	40	3	93% (**3h**)
9	4-CO_2H-C_6H_4 (**1i**)	25	8	98% (**3i**)
10	4-CF_3-C_6H_4 (**1j**)	25	8	85% (**3j**)
11	4-SO_2NH_2-C_6H_4 (**1k**)	25	8	85% (**3k**)
12	3-Me-C_6H_4 (**1l**)	40	3	93% (**3l**)
13	3-Br-C_6H_4 (**1m**)	40	4	93% (**3m**)
14	3-CO_2H-C_6H_4 (**1n**)	25	8	94% (**3n**)
15	2-Me-C_6H_4 (**1o**)	40	3	73% (**3o**)
16	2-NO_2-C_6H_4 (**1p**)	40	4	75% (**3p**)
17	3,4-$(MeO)_2$-C_6H_3 (**1q**)	40	3	88% (**3q**)
18	3-Cl-4-F-C_6H_3 (**1r**)	40	2	82% (**3r**)
19	3,5-Cl_2-C_6H_3 (**1s**)	40	3	85% (**3s**)
20	2,5-F_2-C_6H_3 (**1t**)	40	4	73% (**3t**)

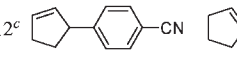
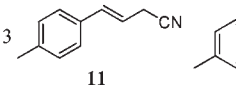
[a] Unless noted otherwise, the reactions were carried out on arylhydrazine (0.3 mmol), *tert*-butyl acrylate (0.6 mmol) with 3.6 mol % of ligand **D** (0.0108 mmol), and 3 mol % of $Pd(OAc)_2$ (0.009 mmol) in PhCl/MeOH (0.4 mL/0.1 mL). [b] Isolated yield.

To further illustrate the utility of this coupling reaction, different acrylates and olefins were evaluated under the optimal reaction conditions (Table 3). As shown in Table 3, the ester moiety of acrylate has little influence on the reaction efficiency. The β-substituent can be present and provide the coupling product with good stereoselectivity (Table 3, entries 7 and 8). Interestingly, acrylic acid as well as acrylamide works well for this reaction to give cross-coupling products in good yields (Table 3, entries 9 and 10). Unactivated olefins such as cyclopentene and 3-butenenitrile are also viable coupling partners suggesting that this reaction is not limited to the activated carbon−carbon double bond (Table 3, entries 12 and 13).

In terms of the mechanism of this transformation, the later stage of it looks like the Heck coupling which involved the aryl palladium complex. It is assumed that the formation of the aryl palladium complex might involve cleavage of the aryl carbon−nitrogen bond. However our initial attempts to obtain the aryl palladium intermediates by using

Table 3. Palladium-Catalyzed Cross-Coupling of Arylhydrazine (**1**) with Various Olefins[a]



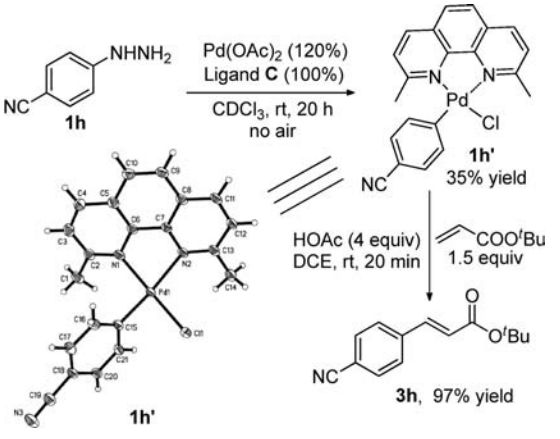
entry	R^1	R^2	R^3	yield (%)[b]
1	R^1= COOH	R^2= H	R^3= COO^nBu	**97% (3u)**
2	R^1= COOH	R^2= H	R^3= COOEt	**96% (3v)**
3	R^1= COOH	R^2= H	R^3= COOMe	**98% (3w)**
4	R^1= CH_3	R^2= H	R^3= COO^nBu	**89% (3x)**
5	R^1= CH_3	R^2= H	R^3= COOEt	**86% (3y)**
6	R^1= CH_3	R^2= H	R^3= COOMe	**84% (3z)**
7	R^1= CH_3	R^2= CH_3	R^3= COOEt	**72% (4)**
8	R^1= CN	R^2= $PhCH_2CH_2$	R^3= COOEt	**45% (5)**
9	R^1= H	R^2= H	R^3= CONHPh	**78% (6)**
10	R^1= H	R^2= H	R^3= COOH	**73% (7)**
11	R^1= H	R^2= H	R^3= Ph	**93% (8)**
12[c]				**80% yield[d] 9 : 10 = 83 : 17**
13				**85% yield[d] 11 : 12 = 84 : 16**

9 10 11 12

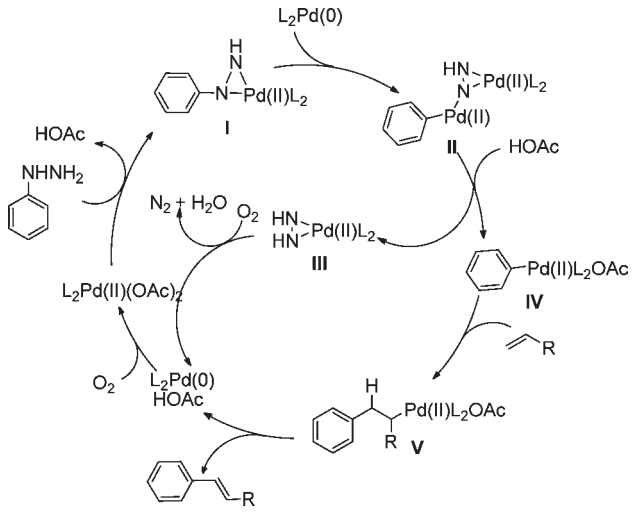
[a] Unless noted otherwise, the reactions were carried out on arylhydrazine (0.3 mmol), alkene **2** (0.6 mmol) with 3.6 mol % of ligand **D** (0.0108 mmol), and 3 mol % of $Pd(OAc)_2$ (0.009 mmol) in PhCl/MeOH (0.4 mL/0.1 mL). [b] Isolated yield. [c] Used cyclopentene. [d] Total yield.

stoichiometric amounts of palladium acetate and ligand in the absence of an olefin partner failed. Fortunately, an analogous palladium chloro complex **1h′** (Scheme 1) was isolated as a stable solid which could be crystallized for the X-ray diffraction study when **1h** was treated with 1.2

Scheme 1. Stiochiometric Reaction of **1h** with $Pd(OAc)_2$ and Ligand **C**



Scheme 2. Proposed Mechanism



equiv of $Pd(OAc)_2$ and 1 equiv of ligand **C** in $CDCl_3$. In addition, this complex readily undergoes a cross-coupling reaction with *tert*-butyl acrylate in excellent yields. The X-ray structure of **1h′** clearly demonstrated that the C−N bond was replaced by a C−Pd bond and provided solid evidence that this reaction involved C−N bond cleavage.

A plausible mechanism involving both Pd(0) and Pd(II) was proposed to rationalize the C−N bond cleavage process (Scheme 2). The existence of palladiaziridine complex **I** was established by Muñiz et al.'s work.[8] It is assumed that both the C−N and N−N bonds in palladiaziridine complex **I** are activated by palladium(II).[9] The formation of palladiaziridine complex **I** is crucial for the catalytic cycle because there is no reaction at all when both nitrogens of phenylhydrazine were protected while single terminal protected phenylhydrazine could give the coupling product in moderate yields (see Supporting Information). The oxidative addition of palladium(0) to the initially formed palladiaziridine complex **I** cleaved the C−N bond to give the two palladium(II) centered complex **II**. Protonolysis of the *in situ* formed complex **II** released the aryl palladium complex **IV** and the palladiaziridine complex **III**, which collapsed to give palladium(0), nitrogen gas, and water in the presence of oxygen. The aryl palladium complex **IV** stabilized by two ligand **D** is the major peak in the absence of olefin. It could be transformed to intermediate **V** in the presence of olefin. Degeneration of intermediate **V** gave a coupling product and regenerated [$L_2Pd(0)$]. The catalytic cycle is closed upon reoxidation of Pd(0) to Pd(II) by air with the assistance of a ligand.

In summary, we have developed the first palladium-catalyzed C−C bond formation of arylhydrazines via aryl C−N bond cleavage with olefins. A possible mechanism involving both Pd(0) and Pd(II) was proposed to rationalize the C−N bond cleavage. This reaction proceeded readily with various aryl hydrazines and acrylates as well as unactivated olefins under very mild conditions. By using the commercially available aryl hydrazines as the coupling partner and 1 atm of air as the environmentally benign oxidant, this cost-effective methodology will be very attractive for both academia and industry. It is foreseeable that this new mode of C−Pd complex formation will spur the development of palladium-catalyzed cross-coupling in the future.

Acknowledgment. We gratefully acknowledge the Nanyang Technological University and Singapore Ministry of Education Academic Research Fund (MOE2011-T2-1-013) for the funding of this research. We thank Profs. K. Narasaka (NTU) and S. Chiba (NTU) for their helpful discussions.

Supporting Information Available. Additional experimental procedures, spectrum data for reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

(8) Muñiz, K.; Nieger, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2305–2308.

(9) The C−N bond length in palladiaziridine crystal CCDC-288043 is 1.401 Å, which is significantly longer than 1.346 Å, a common C−N bond length.