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Synthesis of Nonsubstituted Anilines from Molecular Nitrogen via Transmetalation of Arylpalladium Complex with Titanium−Nitrogen Fixation Complexes

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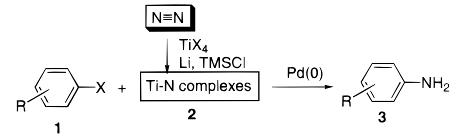
Since Migita[1] succeeded in synthesizing disubstituted aniline derivatives from arylpalladium complex and dialkylstannane, a method for synthesizing mono- and disubstituted aniline derivatives from aryl halides using palladium catalyst has been established by the ingenious studies of Buchwald and Hartwig.[2] However, synthesis of nonsubstituted aniline derivatives from arylpalladium complex was not known because we must use NH_3 for that purpose. These results have stimulated us to synthesize nonsubstituted aniline derivatives[2v,3] by a one-step reaction from arylpalladium complex and titanium−nitrogen fixation complexes prepared from *molecular nitrogen* and the $TiCl_4$- or $Ti(OiPr)_4$−Li−TMSCl system (Scheme 1).[4]

If titanium−nitrogen fixation complexes **2** are transmetalated with ArPdX **4**, arylpalladium−nitrogen complex **5** would be formed, and this should be followed by reductive elimination to give nonsubstituted aniline derivatives **3** (Scheme 2).

Scheme 1



Scheme 2

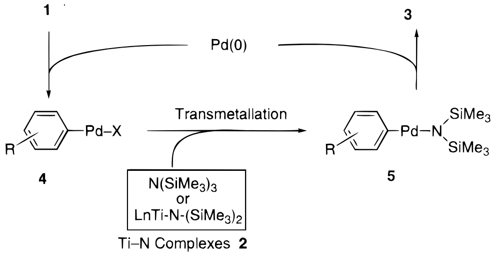
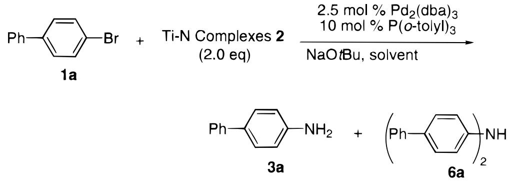


Table 1. Ligand Effects on Palladium-Catalyzed Amination of **1a**[a]

				yields (%)	
run	ligand	solvent	time (h)	**3a**	**6a**
1	P(*o*-tolyl)$_3$	THF	24	0	0
2	P(*o*-tolyl)$_3$	toluene	4	32	11
3	P(*o*-tolyl)$_3$	toluene	44	23	28
4	(*S*)-BINAP	toluene	40	39	4
5	DPPF	toluene	21	30	0
6	DPPP	toluene	23	14	0
7	(*S*)-BINAPO	toluene	21	15	0

[a] All reactions were carried out in the presence of 2.5 mol % $Pd_2(dba)_3$, 5−10 mol % ligand, 2 equiv of Ti−N complexes, and 2.8 equiv of NaO*t*Bu in toluene at 90 °C.

Scheme 3



When a THF solution of titanium−nitrogen complexes **2** (2.0 equiv), which was prepared from $Ti(OiPr)_4$ (2.0 equiv), Li (20 equiv), and TMSCl (20 equiv) in THF under an atmosphere of nitrogen at room temperature for 8 h,[4] was added to a THF solution of $Pd_2(dba)_3\cdot CHCl_3$ (2.5 mol %), P(*o*-tolyl)$_3$ (10 mol %), and NaO*t*Bu (2.8 equiv), and the solution was refluxed overnight, no nitrogen-containing products were produced and a dehalogenation product was obtained along with the starting material (Table 1, run 1). Since it is known that THF is not the best solvent for palladium-catalyzed amination,[2a,b] the solvent was changed from THF to toluene and the reaction was carried out in a similar manner. As a result, we obtained 4-aminobiphenyl **3a** in 32% yield along with secondary aniline **6a** in 11% yield (run 2) (Scheme 3). The result indicates that nonsubstituted aniline could be synthesized from aryl halide and molecular nitrogen by a one-step reaction using palladium-catalyzed amination.[5] Various ligands were used for this reaction, and the results are shown in Table 1. The longer reaction time increased the yield of the secondary aniline **6a** (run 3), and the use of (*S*)-BINAP as a ligand gave good results (run 4). It seems likely that the bidentate ligand predominantly gave primary aniline **3a** (runs 4−7).

NaO*t*Bu was essential in this reaction, and if the reaction was carried out in the presence of CsF[6] instead of NaO*t*Bu, the desired product was not obtained. Various aryl bromides were used for this reaction (Table 3, method A). The electron-donating group accelerated the formation of secondary anilines **6** (runs 2, 3, and 4), while the aryl bromide having the electron-withdrawing group

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(1) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

(2) (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348. (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. (c) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708. (d) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598. (e) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030. (f) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133. (g) Hartwig, J. F.; Richards, S.; Baranano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626. (h) Wolfe, J. P.; Wagaw. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (i) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. (j) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525. (k) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240. (l) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109. (m) Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics* **1996**, *15*, 2794. (n) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264. (o) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268. (p) Marcoux, J. F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568. (q) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054. r) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232. (s) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451. (t) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807. (u) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066. (v) Wolfe, J. P.; Ahmman, J.; Sadigihi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367. (w) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359.

(3) Synthesis of nonsubstituted aniline derivatives from aryl halides and imine or allylamine derivative followed by hydrolysis (two steps) has been developed. See ref 2v. See also: (a) J-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313. (b) Mann, G.; Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 827.

(4) (a) Kawaguchi, M.; Hamaoka, S.; Mori, M. *Tetrahedron Lett.* **1993**, *34*, 6907. (b) Mori, M.; Kawaguchi, M.; Hamaoka, S. *Heterocycles* **1994**, *39*, 729. (c) Hori, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 1480. (d) Mori, M.; Hori, K.; Akashi, M.; Hori, M.; Nishida, M.; Sato, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 636.

(5) It has been reported that the reaction of excess PhLi with molecular N_2 (1−100 atm) in the presence of Cp_2TiCl_2 gave aniline (3−15% yield based on Cp_2TiCl_2). (a) Vol'pin, M. E.; Shur, V. B.; Kudryavtsev, R. V.; Prodayko, L. A. *Chem. Commum.* **1968**, 1038. (b) Vol'pin, M. E. *J. Organomet. Chem.* **1980**, *200*, 319.

(6) Since it was considered that the main species of titanium−nitrogen complex is N(TMS)$_3$ at this stage, CsF was used because we usually added CsF in the reaction of titanium−nitrogen complexes **2** with organic compounds.[4]

S0002-7863(98)01465-6 CCC: $15.00

Scheme 4

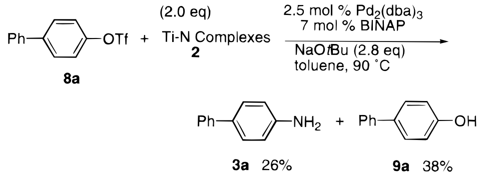


Table 2. Palladium-Catalyzed Amination of **8a** under Various Conditions[a]

run	cat.	ligand	temp (°C)	time (h)	yield (%)	
					3a	**9**
1[b]	$Pd_2(dba)_3$	(*S*)-BINAP	90	4	26	38
2	$Pd_2(dba)_3$	(*S*)-BINAP	90	4	21	8
3	$Pd(OAc)_2$	(*S*)-BINAP	90	4	31[c]	14
4	$Pd(OAc)_2$	DPPF	90	4	41	3
5	$Pd_2(dba)_3$	DPPF	90	4	45	8
6	$Pd_2(dba)_3$	DPPF	70	4	53	10
7	$Pd_2(dba)_3$	DPPF	50	23	46	4
8	$Pd_2(dba)_3$	P(*o*-tolyl)$_3$	90	4	0	<14
9[d]	$Pd_2(dba)_3$	DPPF	70	2	73	9

[a] 4-Bipheny triflate **8a** was added dropwise to a mixture of $Pd_2(dba)_3$ (2.5 mol %) or $Pd(OAc)_2$ (5 mol %), ligand (7 mol %), NaO*t*Bu (1.4 equiv), and Ti−N complexes (2.0 equiv) in THF over 20 min. The concentration of the solution was 0.05 M. [b] 2.8 equiv of NaO*t*Bu was used, and the substrate was not added slowly. The concentration of solution was 0.10 M. [c] 4% **6a** was obtained. [d] The reaction conditions are the same as those of footnote *a*, except that 2.8 equiv of NaO*t*Bu was used and the substrate was added slowly over 1 h.

predominantly gave the primary anilines (runs 5 and 6). It was quite interesting that the desired aniline derivative **3g** was obtained from hindered aryl bromide **1g** in 47% yield along with secondary aniline **6g** in 16% yield (run 7).

Subsequently, aryl triflate **8a** was used for this reaction under the same reaction conditions. As a result, a fair amount of phenol **9** was produced along with the desired aniline derivative **3a** (Scheme 4).[2n,o]

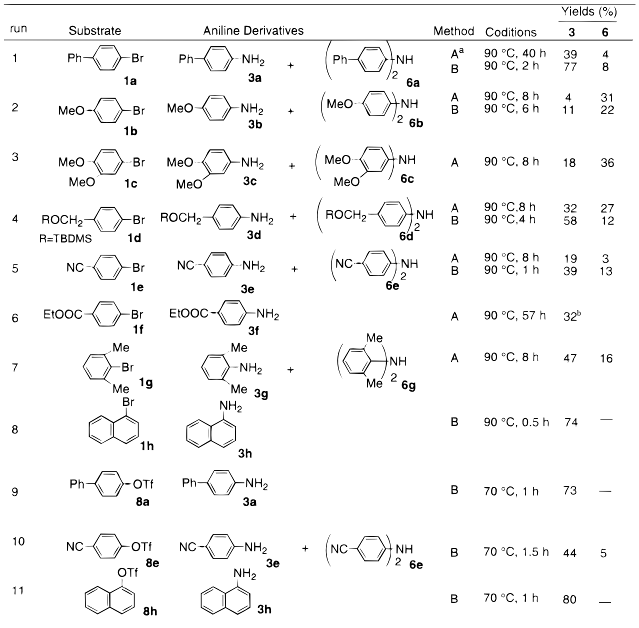
Since it is already known that the formation of phenol is due to NaO*t*Bu attacking the O−S bond of triflate, the reaction conditions described by Buchwald and Hartwig[2n,o] were slightly modified (NaO*t*Bu, 1.4 equiv; concentration of the substrate, from 0.1 to 0.05 M, and slow addition of the substrate). It was found that the slow addition of the substrate was important for preventing the formation of phenol (Table 2, run 2), and the use of $Pd_2(dba)_3$ and DPPF gave good results (run 5).

The lower reaction temperature raised the yield of **3a** (run 6). Finally, when a large amount of NaO*t*Bu was used for this reaction (run 9), **3a** was produced in 73% yield.

We reinvestigated whether the slow addition of the substrate was effective or not for the reaction of aryl bromides with **2**. As a result, it was quite effective and the desired aniline **3a** was obtained in 77% yield (Table 3, run 1, method B). Various aryl bromides and aryl triflates were examined, and the results are shown in Table 3 (method B). These results indicate that titanium−nitrogen complexes **2** can be used for the synthesis of nonsubstituted anilines **3**.

To estimate the species of the reaction intermediate, $N(TMS)_3$ or $HN(TMS)_2$ was used instead of titanium−nitrogen complexes **2** for this reaction, but no nitrogen-containing products were obtained. This indicates that the active species would be titanium−nitrogen complex, not $N(TMS)_3$, and transmetalation of the nitrogen moiety from titanium to palladium is an important process for this reaction.[7] The possible reaction course is shown in Scheme 5.

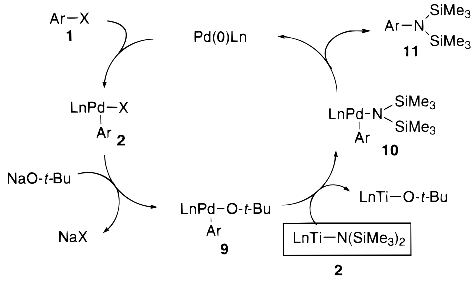
Table 3. Palladium-Catalyzed Amination of Aryl Bromides and Aryl Triflates with Ti−N Complexes[a]



run	Substrate	Aniline Derivatives	Method	Coditions	Yields (%)	
					3	**6**
1	**1a**	**3a** + **6a**	A[a] B	90 °C, 40 h 90 °C, 2 h	39 77	4 8
2	**1b**	**3b** + **6b**	A B	90 °C, 8 h 90 °C, 6 h	4 11	31 22
3	**1c**	**3c** + **6c**	A	90 °C, 8 h	18	36
4	**1d** R=TBDMS	**3d** + **6d**	A B	90 °C,8 h 90 °C,4 h	32 58	27 12
5	**1e**	**3e** + **6e**	A B	90 °C, 8 h 90 °C, 1 h	19 39	3 13
6	**1f**	**3f**	A	90 °C, 57 h	32[b]	
7	**1g**	**3g** + **6g**	A	90 °C, 8 h	47	16
8	**1h**	**3h**	B	90 °C, 0.5 h	74	—
9	**8a**	**3a**	B	70 °C, 1 h	73	—
10	**8e**	**3e** + **6e**	B	70 °C, 1.5 h	44	5
11	**8h**	**3h**	B	70 °C, 1 h	80	—

[a] **Method A:** Reactions were carried out in the presence of 2.5 mol % $Pd_2(dba)_3$, 5−10 mol % ligand, 2 equiv of Ti−N complexes, and 2.8 equiv of NaO*t*Bu in toluene at 90 °C. **Method B:** The substrate in toluene was added dropwise to a toluene solution of $Pd_2(dba)_3$ (2.5 mol %), DPPF (7 mol %), NaO*t*Bu (2.8 equiv), and Ti−N complexes (2.0 equiv) over 1 h, and the solution was heated. (a) (*S*)-BINAP was used as the ligand. (b) 2% isopropyl 4-aminobenzoate was contained.

Scheme 5. Possible Reaction Mechanism



In conclusion, nonsusbstituted anilines could be synthesized from aryl bromides or aryl triflates and *molecular nitrogen as nitrogen source* using palladium catalyst.

Further studies on the mechanism and applications of this reaction are now in progress.

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Supporting Information Available: Experimental procedures and NMR spectra for **3d**, **6c**, **6d**, and **6g** (7 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(7) In this reaction, a fair amount of secondary aniline **6** was obtained, and a longer reaction time increased the yield of **6**. We could not explain the formation of secondary aniline **6** by transmetalation because $N(TMS)_3$ and $NH(TMS)_2$ could not transmetalate to arylpalladium complex. Probably, $ArN(TMS)_2$ does not transmetalate with arylpalladium complex. It means that the active species of titanium−nitrogen complex may be LnTi═NTMS.