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Communication

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Weizhi Geng, Wen-Xiong Zhang, Wei Hao, and Zhenfeng Xi

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Cyclopentadiene-Phosphine/Palladium Catalyzed Cleavage of C-N Bonds in Secondary Amines: Synthesis of Pyrrole and Indole Derivatives from Secondary Amines and Alkenyl or Aryldibromides

Weizhi Geng,[†] Wen-Xiong Zhang,[†] Wei Hao,[†] Zhenfeng Xi[*,†,‡]

Beijing National Laboratory for Molecular Sciences (BNLMS), and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China; State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry (SIOC), Shanghai 200032, China

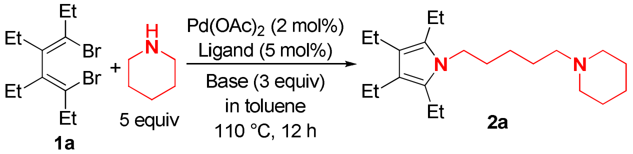
Supporting Information Placeholder

Abstract: An efficient Pd–catalyzed cleavage of C(sp^3)–N bonds in secondary amines and consequent C(sp^2)–N and C(sp^3)–N coupling process was developed. Various secondary amines could be used to react with alkenyl or aryl dibromides affording pyrroles and indoles in high yields. Cyclopentadiene-phosphine ligands, a new type of P–olefin ligands, were found to be able to remarkably promote the efficiency of this Pd–catalyzed process. A reactive Pd complex coordinated with a cyclopentadiene-phosphine ligand was successfully isolated and structurally characterized.

The cleavage of carbon–nitrogen (C–N) bonds is of significant synthetic interest, because such bonds are common in organic chemistry and usually unreactive.[1-8] The cleavage of such C–N bonds in tertiary amines have been reported leading to various important N-heterocycles by using a stoichiometric amount[3] or a catalytic amount of transition-metal complexes.[4-6] However, to the best of our knowledge, there is no report in the literature on transition-metal catalyzed cleavage and synthetic applications of C(sp^3)–N bonds in secondary amines.[1b,7,8] Since a secondary amine contains one N–H bond and two C–N bonds, their efficient selective cleavage and further synthetic applications are very attractive for both mechanistic study and synthetic chemistry. Herein, we report the first example of catalytic cleavage of the C(sp^3)–N bonds in secondary amines and consequent C(sp^2)–N and C(sp^3)–N coupling process, which results in high-yield formation of pyrroles and indoles. In addition, cyclopentadiene-phosphine ligands, a new type of mixed P-olefin ligands,[9,10] were synthesized and found to be able to remarkably promote the efficiency of this catalytic process.

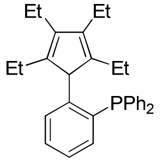
As shown in Table 1, when the dibromide **1a**[11] was treated with piperidine, an unexpected pyrrole derivative **2a** was obtained. Obviously, an unprecedented coupling process involving amination, C–N bond cleavage and C–N bond formation took place.

Table 1. Optimization of Reaction Conditions

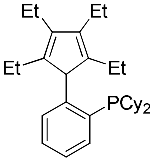


entry	ligand	base	yield of **2a** (%)^a
1	–	LiO*t*-Bu	0
2	PPh$_3$	LiO*t*-Bu	32
3	Xantphos	LiO*t*-Bu	0
4	Xphos	LiO*t*-Bu	18
5	Sphos	LiO*t*-Bu	29
6	Davephos	LiO*t*-Bu	16
7	L1	LiO*t*-Bu	75 (62)
8	L2	LiO*t*-Bu	52
9	L3	LiO*t*-Bu	0
10	L4	LiO*t*-Bu	38
11	L1	NaO*t*-Bu	0
12	L1	KO*t*-Bu	0
13	L1	K$_3$PO$_4$	14
14	L1	Cs$_2$CO$_3$	0

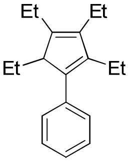
^{a} GC yields. Isolated yields are in parenthesis.



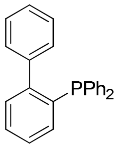
L1



L2



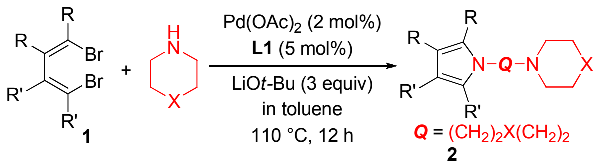
L3

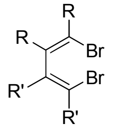
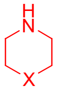
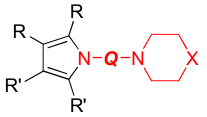
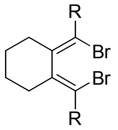
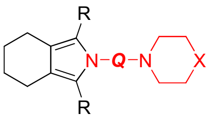
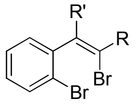
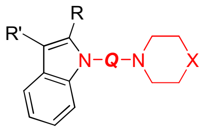
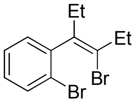
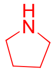
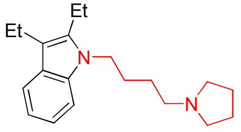


L4

After various reaction conditions being screened, we found that our newly designed and synthesized phosphine–cyclopentadiene ligands (**L1**, **L2**, see SI for detailed synthetic procedure) were the best for this reaction (entries 7, 8). Many other ligands, including those commonly used ones such as PPh$_3$, Xantphos, Xphos, Sphos, and Davephos gave low yields or totally no products (entries 2-6). Ligands such as **L3** and **L4** also showed very low or totally no efficiency (entries 9, 10). These results demonstrated that both the P moiety and the cyclopentadiene moiety were necessary for high efficiently realizing this Pd-catalyzed coupling process. In addition, base was very sensitive for this transformation and LiO*t*-Bu was found most effective. An excess amount of piperidine (more than 5 equivalents) is required to achieve a clean reaction. The optimal reaction condition was realized as follows (see SI for details): Pd(OAc)$_2$ (2 mol%), **L1** (5 mol%), LiO*t*-Bu (3 equiv), in piperidine/toluene = 1/9 (2 mL) solvent, 110 °C, 12 h (entry 7). With this optimized condition, the pyrrole derivative **2a** was obtained in 62% isolated yield.

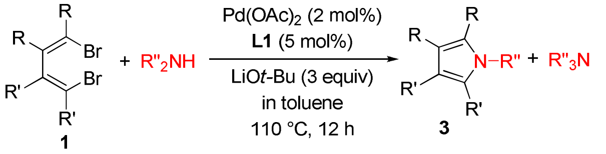
Table 2. Palladium-Catalyzed Reaction of Dibromides **1** with Cyclic Amines

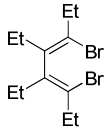
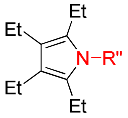
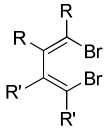
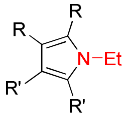
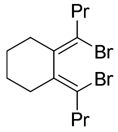
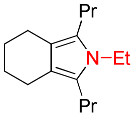
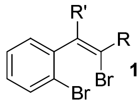
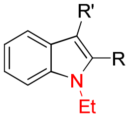


dibromide **1**	cyclic amine	product **2**
 **1a:** R = R' = Et **1b:** R = R' = Pr **1c:** R = Et, R' = Ph	 **X** = CH$_2$, O	 **2a:** R = R' = Et, **X** = CH$_2$, 62% **2b:** R = R' = Et, **X** = O, 76% **2c:** R = R' = Pr, **X** = CH$_2$, 85% **2d:** R = Et, R' = Ph, **X** = CH$_2$, 84%
 **1d:** R = Et **1e:** R = Pr	**X** = CH$_2$, O	 **2e:** R = Et, **X** = CH$_2$, 77% **2f:** R = Pr, **X** = CH$_2$, 90% **2g:** R = Pr, **X** = O, 82%
 **1f:** R = TMS, R' = Me **1g:** R = R' = Et **1h:** R = R' = Pr	**X** = CH$_2$, O, CHCH$_3$	 **2h:** R = TMS, R' = Me, **X** = CH$_2$, 64% **2i:** R = R' = Et, **X** = CH$_2$, 81% **2j:** R = R' = Et, **X** = O, 86% **2k:** R = R' = Et, **X** = CHCH$_3$, 79% **2l:** R = R' = Pr, **X** = CH$_2$, 85%
 **1g**		 **2m**: 58%

The scope of the above Pd-catalyzed coupling process was investigated under the optimized reaction conditions. Results are summarized in Tables 2-4. A variety of dibromides **1a-h** were applied. Shown in Table 2 are results obtained from the reaction of dibromides **1a-h** with various cyclic secondary amines, including piperidine, 4-methyl piperidine, morpholine, and pyrrolidine. A wide variety of the pyrrole derivatives **2a-d**, the 4,5,6,7-tetrahydro-isoindole derivatives **2e-g**, and the indole derivatives **2h-m** were obtained in good to excellent isolated yields. In addition, acyclic secondary amines including Et$_2$NH, Pr$_2$NH, Bu$_2$NH and *i*-Pr$_2$NH were investigated and results are summarized in Table 3. No reaction took place when *i*-Pr$_2$NH was used (the dibromide **1a** was unreacted), probably due to the steric effect. It should be noted that formation of R″$_3$N was observed in all these reactions. For example, when **1a** was treated with Pr$_2$NH, Pr$_3$N was formed in 85% GC yield, along with **3b** in 69% isolated yield. The formation of R″$_3$N sheds clue on the reaction mechanism.

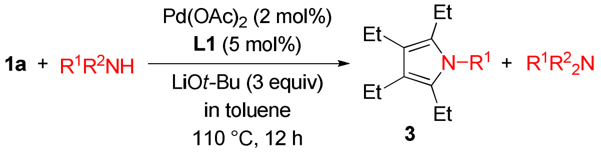
Table 3. Palladium-Catalyzed Reaction of Dibromides **1** with Dialkylamines (R″$_2$NH)

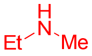
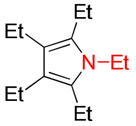
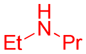
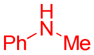
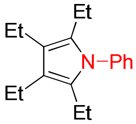


dibromide **1**		amine	product **3**	
	**1a**	R"$_2$NH		**3a:** R" = Et, 71% **3b:** R" = Pr, 69% Pr$_3$N: 85% (GC) **3b'**: R" = *i*-Pr, 0% **3c:** R" = *n*-Bu, 77%
	**1b,c**	Et$_2$NH		**3d:** R = R' = Pr, 53% **3e:** R = Et, R' = Ph, 63%
	**1e**	Et$_2$NH		**3f:** 50%
	**1f-1h**	Et$_2$NH		**3g:** R = TMS, R' = Me, 63% **3h:** R = R' = Et, 83% **3i:** R = R' = Pr, 80%

We then applied acyclic secondary amines possessing two different groups (R^{1}R^{2}NH), with the aim to investigate the chemoselective cleavage of C(sp^3)–N bonds. As given in Table 4, when the dibromide **1a** was treated with Me(Et)NH, the *N*-Et pyrrole derivative **3a** was obtained in 65% isolated yield as the only pyrrole derivative product. Obviously, a selective cleavage of the Me-N bond in Me(Et)NH took place. In the case of Et(Pr)NH, a mixture of two pyrrole derivatives **3a** and **3b** was formed in 2:3 ratio. When Me(Ph)NH was used, the cleavage took place exclusively at the weaker Me-N bond (71.4 kcal/mol for the bond energy of Me-N, 100.1 kcal/mol for the bond energy of Ph-N),[12a,b] affording the corresponding *N*-Ph pyrrole derivative **3j** in 57% isolated yield. In addition, the tertiary amine Me$_2$NPh was formed in 75% GC yield. In contrast, when Et(Ph)NH was used, no remarkable reaction took place. These results demonstrate that the bulkiness of the *N*-substituent and the C-N bond energy determine which C-N bond in R^{1}R^{2}NH is more readily cleaved.[12] The formation of Me$_2$NPh again sheds clue on the reaction mechanism.

Table 4. Investigation into the Selectivity of Amines with Two Different Substituents (R^1R^2NH)



entry	R^1R^2NH	product **3**	
1			**3a:** 65%
2		**3a + 3b**	**3a**:**3b** = 2:3 total yield 62%
3			**3j:** 57% Me_2NPh: 75% (GC)

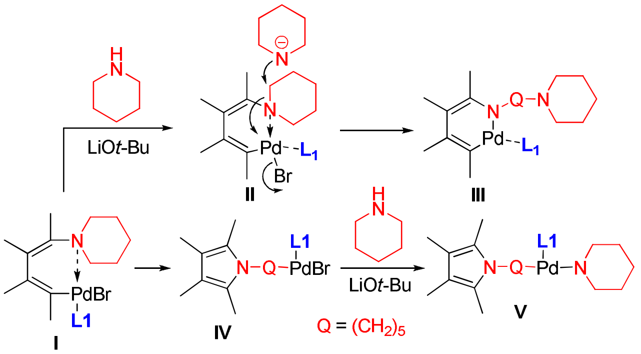
It is obvious that the new type of mixed P-olefin ligands is very effective for this Pd-catalyzed coupling process. However, it is not clear yet how this ligand works together with the palladium. Given in Scheme 1 are proposed key intermediates. The intermediate **I** would be formed from a dibromide **1** and a secondary amine, *via* oxidative addition/amination/oxidative addition process.[13] Nucleophilic attack of piperidine anion on intermediate **I** would generate a 6-membered palladacycle **III**, which could then reductively eliminate to form the product. Although this mechanism is readily acceptable, however, the path *via* intermediates **IV** and **V** is also possible,[14,15] since the compound **4**, which might be formed *via* reductive elimination of **IV**,[15] was obtained when less amount of morpholine was used (Scheme 2). Under the same reaction condition, the compound **5**, a precursor of **I**, could give **2i** in 90% isolated yield with piperidine. In sharp contrast, no formation of **2i** was observed without piperidine; A trace amount of de-iodination product and a small amount (<3%) of **6** were observed. When Et_2NH was used, the indole derivative **7** was obtained. These results indicate that the proposed intermediate **IV** is possible, but its formation is a slow step and its following reaction with amine would facilitate its formation.

Further, as shown in Eq. 1, a Pd-**L1** complex **8** was obtained and structurally characterized (see SI for details). The complex **8** is a dimer with two bridging chloride atoms. The five-membered cyclometallated ring is puckered and the bite angle of C_σ–Pd–P is 84.7(3)°. The bond length of the Pd–C_σ bond is 2.090(10)Å, similar to other five-membered azapalladacycles.[16]

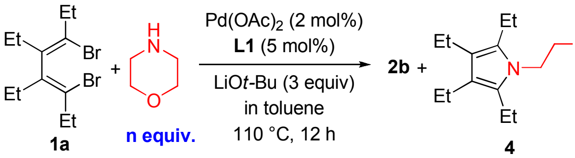
Notably, this complex **8** (2 mol%) could catalyze efficiently the coupling process of **1a** or **1g** with piperidine to give **2a** and **2i** in 62% and 83% isolated yields, respectively.

In summary, we have developed the first transition-metal catalyzed cleavage of C(sp^3)–N bonds in secondary amines. A new type of cyclopentadiene-phosphine ligands were found to be able to remarkably promote the efficiency of this catalytic process. This finding represents an unprecedented way for the synthesis of a wide variety of pyrrole and indole derivatives with useful *N*-substitution.[17] Further study on the reaction mechanism and synthetic applications is in progress.

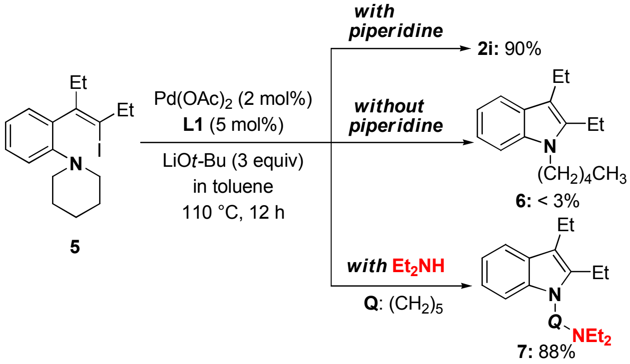
Scheme 1. Proposed Key Intermediates

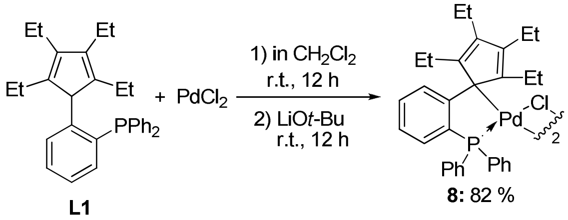


Scheme 2. Mechanistic Study



morpholine **n** equivalents	yield of **2b**	yield of **4**
n = 5	76%	trace
n = 2	52%	11%
n = 1	27%	19%





(1)

ASSOCIATED CONTENT

Supporting Information. Experimental details, X-ray data for **L1**, **8** and scanned NMR spectra of all new products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

zfxi@pku.edu.cn

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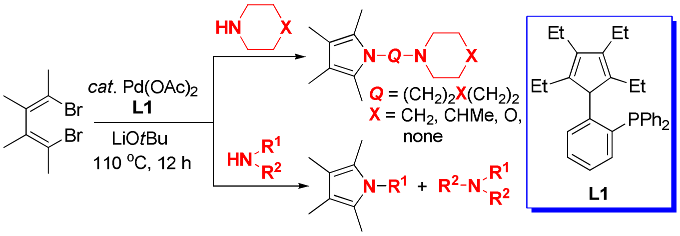
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X = CH2, CHMe, O, none
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N–R1 + R2–N R1 R2
Et
Et
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PPh2
L1